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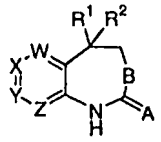

(I)

(57) Abstract

The present invention relates to 1,3-benzodiazepin-2-ones and 1,3-benzoxazepin-2-ones of formula (I) or stereoisomeric forms, stereoisomeric mixtures, or pharmaceutically acceptable salt forms thereof, which are useful as inhibitors of HIV reverse transcriptase, and to pharmaceutical compositions and diagnostic kits comprising the same, and methods of using the same for treating viral infection or as an assay standard or reagent.

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TITLE

1,3-BENZODIAZEPIN-2-ONES AND 1,3-BENZOXAZEPIN-2-ONES USEFUL AS HIV REVERSE TRANSCRIPTASE INHIBITORS

FIELD OF THE INVENTION

This invention relates generally to 1,3-benzodiazepin-2-ones and 1,3-benzoxazepin-2-ones which are useful as inhibitors of HIV reverse transcriptase, pharmaceutical compositions and diagnostic kits comprising the same, methods of using the same for treating viral infection or as assay standards or reagents, and intermediates and processes for making the same.

BACKGROUND OF THE INVENTION

Two distinct retroviruses, human immunodeficiency virus (HIV) type-1 (HIV-1) or type-2 (HIV-2), have been etiologically linked to the immunosuppressive disease, acquired immunodeficiency syndrome (AIDS). HIV seropositive individuals are initially asymptomatic but typically develop AIDS related complex (ARC) followed by AIDS. Affected individuals exhibit severe immunosuppression which predisposes them to debilitating and ultimately fatal opportunistic infections.

The disease AIDS is the end result of an HIV-1 or HIV-2 virus following its own complex life cycle. The virion life cycle begins with the virion attaching itself to the host human T-4 lymphocyte immune cell through the bonding of a glycoprotein on the surface of the virion's protective coat with the CD4 glycoprotein on the lymphocyte cell. Once attached, the virion sheds its glycoprotein coat, penetrates into the membrane of the host cell, and uncoats its RNA. The virion enzyme, reverse transcriptase, directs the process of transcribing the RNA into single-stranded DNA. The viral RNA is degraded and a second DNA strand is created. The now double-stranded DNA is integrated into the

human cell's genes and those genes are used for virus reproduction.

At this point, RNA polymerase transcribes the integrated DNA into viral RNA. The viral RNA is translated into the precursor *gag-pol* fusion polyprotein. The polyprotein is then cleaved by the HIV protease enzyme to yield the mature viral proteins. Thus, HIV protease is responsible for regulating a cascade of cleavage events that lead to the virus particle's maturing into a virus that is capable of full infectivity.

The typical human immune system response, killing the invading virion, is taxed because the virus infects and kills the immune system's T cells. In addition, viral reverse transcriptase, the enzyme used in making a new virion particle, is not very specific, and causes transcription mistakes that result in continually changed glycoproteins on the surface of the viral protective coat. This lack of specificity decreases the immune system's effectiveness because antibodies specifically produced against one glycoprotein may be useless against another, hence reducing the number of antibodies available to fight the virus. The virus continues to reproduce while the immune response system continues to weaken. Eventually, the HIV largely holds free reign over the body's immune system, allowing opportunistic infections to set in and without the administration of antiviral agents, immunomodulators, or both, death may result.

There are at least three critical points in the virus's life cycle which have been identified as possible targets for antiviral drugs: (1) the initial attachment of the virion to the T-4 lymphocyte or macrophage site, (2) the transcription of viral RNA to viral DNA (reverse transcriptase, RT), and (3) the processing of gag-pol protein by HIV protease.

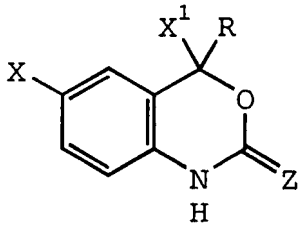
Inhibition of the virus at the second critical point, the viral RNA to viral DNA transcription process, has

provided a number of the current therapies used in treading AIDS. This transcription must occur for the virion to reproduce because the virion's genes are encoded in RNA and the host cell reads only DNA. By introducing drugs that block the reverse transcriptase from completing the formation of viral DNA, HIV-1 replication can be stopped.

A number of compounds that interfere with viral replication have been developed to treat AIDS. For example, nucleoside analogs, such as 3'-azido-3'-deoxythymidine (AZT), 2',3'-dideoxycytidine (ddC), 2',3'-dideoxythymidinene (d4T), 2',3'-dideoxyinosine (ddI), and 2',3'-dideoxy-3'-thia-cytidine (3TC) have been shown to be relatively effective in halting HIV replication at the reverse transcriptase (RT) stage.

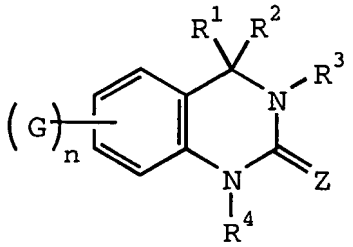
An active area of research is in the discovery of non-nucleoside HIV reverse transcriptase inhibitors. As an example, it has been found that certain benzoxazinones and quinazolinones are active in the inhibition of HIV reverse transcriptase, the prevention or treatment of infection by HIV and the treatment of AIDS.

U.S. 5,519,021 describe reverse transcriptase inhibitors which are benzoxazinones of the formula:



wherein X is a halogen, Z may be O.

EP 0,530,994 and WO 93/04047 describe HIV reverse transcriptase inhibitors which are quinazolinones of the formula A:



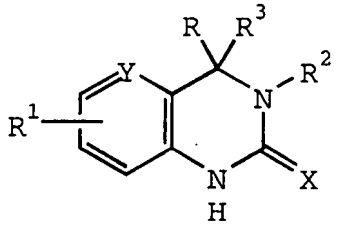
A

wherein G is a variety of groups, R^3 and R^4 may be H, Z may be O, R^2 may be unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted cycloalkyl, unsubstituted heterocycle, and optionally substituted aryl, and R^1 may be a variety of groups including substituted alkyl.

WO 95/12583 also describes HIV reverse transcriptase inhibitors of formula A. In this publication, G is a variety of groups, R^3 and R^4 may be H, Z may be O, R^2 is substituted alkenyl or substituted alkynyl, and R^1 is cycloalkyl, alkynyl, alkenyl, or cyano. WO 95/13273 illustrates the asymmetric synthesis of one of the compounds of WO 95/12583, (S)-(-)-6-chloro-4-cyclopropyl-3,4-dihydro-4((2-pyridy)ethynyl)-2(1H)-quinazolinone.

Synthetic procedures for making quinazolinones like those described above are detailed in the following references: Houpis et al, *Tetr. Lett.* **1994**, *35(37)*, 6811-6814; Tucker et al, *J. Med. Chem.* **1994**, *37*, 2437-2444; and, Huffman et al, *J. Org. Chem.* **1995**, *60*, 1590-1594.

DE 4,320,347 illustrates quinazolinones of the formula:



wherein R is a phenyl, carbocyclic ring, or a heterocyclic ring. Compounds of this sort are not considered to be part of the present invention.

Even with the current success of reverse transcriptase inhibitors, it has been found that HIV patients can become resistant to a single inhibitor. Thus, it is desirable to develop additional inhibitors to further combat HIV infection.

SUMMARY OF THE INVENTION

Accordingly, one object of the present invention is to provide novel reverse transcriptase inhibitors.

It is another object of the present invention to provide a novel method of treating HIV infection which comprises administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt form thereof.

It is another object of the present invention to provide a novel method of treating HIV infection which comprises administering to a host in need thereof a therapeutically effective combination of (a) one of the compounds of the present invention and (b) one or more compounds selected form the group consisting of HIV reverse transcriptase inhibitors and HIV protease inhibitors.

It is another object of the present invention to provide pharmaceutical compositions with reverse transcriptase inhibiting activity comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt form thereof.

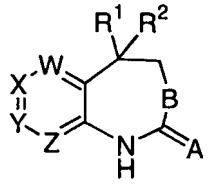
It is another object of the present invention to provide a method of inhibiting HIV present in a body fluid sample which comprises treating the body fluid sample with an effective amount of a compound of the present invention.

It is another object of the present invention to provide a kit or container containing at least one of the compounds of the present invention in an amount effective for use as a standard or reagent in a test or assay for determining the ability of a potential pharmaceutical to inhibit HIV reverse transcriptase, HIV growth, or both.

It is another object of the present invention to provide novel compounds for use in therapy.

It is another object of the present invention to provide the use of novel compounds for the manufacture of a medicament for the treatment of HIV.

These and other objects, which will become apparent during the following detailed description, have been achieved by the inventors' discovery that compounds of formula (I):

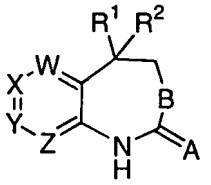


I

wherein R^1, R^2, R^3, X, and Y are defined below, stereoisomeric forms, mixtures of stereoisomeric forms, or pharmaceutically acceptable salt forms thereof, are effective reverse transcriptase inhibitors.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[1] Thus, in an embodiment, the present invention provides a novel compound of formula I:



I

or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein:

A is O or S;

B is selected from O, S, and NR^8;

W is N or CR^3;

X is N or CR^{3a};

Y is N or CR^{3b};

Z is N or CR^{3c};

provided that if two of W, X, Y, and Z are N, then the remaining are other than N;

R^1 is selected from the group C_{1-3} alkyl substituted with 0-7 halogen and cyclopropyl;

R^2 is selected from the group $-R^{2c}$, $-OR^{2c}$, $-OCHR^{2a}R^{2b}$, $-OCH_2CHR^{2a}R^{2b}$, $-O(CH_2)_2CHR^{2a}R^{2b}$, $-OCHR^{2a}C=C-R^{2b}$, $-OCHR^{2a}C=R^{2c}$, $-OCHR^{2a}C\equiv C-R^{2b}$, $-SR^{2c}$, $-SCHR^{2a}R^{2b}$, $-SCH_2CHR^{2a}R^{2b}$, $-S(CH_2)_2CHR^{2a}R^{2b}$, $-SCHR^{2a}C=C-R^{2b}$, $-SCHR^{2a}C=R^{2c}$, $-SCHR^{2a}C\equiv C-R^{2b}$, $-NR^{2a}R^{2c}$, $-NHCHR^{2a}R^{2b}$, $-NHCH_2CHR^{2a}R^{2b}$, $-NH(CH_2)_2CHR^{2a}R^{2b}$, $-NHCHR^{2a}C=C-R^{2b}$, $-NHCHR^{2a}C=R^{2c}$, and $-NHCHR^{2a}C\equiv C-R^{2b}$;

R^{2a} is selected from the group H, CH_3, CH_2CH_3, $CH(CH_3)_2$, and $CH_2CH_2CH_3$;

R^{2b} is H or R^{2c};

R^{2c} is selected from the group C_{1-6} alkyl substituted with 0-2 R^4, C_{2-5} alkenyl substituted with 0-2 R^4, C_{2-5} alkynyl substituted with 0-1 R^4, C_{3-6} cycloalkyl substituted with 0-2 R^{3d}, phenyl substituted with 0-2 R^{3d}, and 3-6 membered heterocyclic group containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^{3d};

alternatively, the group $-NR^{2a}R^{2c}$ represents a 4-7 membered cyclic amine, wherein 0-1 carbon atoms are replaced by O or NR^5;

R^3 is selected from the group H, C_{1-4} alkyl, -OH, C_{1-4} alkoxy, OCF_3, F, Cl, Br, I, $-NR^5R^{5a}$, $-NO_2$, -CN, $-C(O)R^6$, $-NHC(O)R^7$, $-NHC(O)NR^5R^{5a}$, $-NHSO_2R^{10}$, $-SO_2NR^5R^{5a}$, and a 5-6 membered heteroaromatic ring containing 1-4 heteroatoms selected from the group O, N, and S;

R^{3a} is selected from the group H, C_{1-4} alkyl, -OH, C_{1-4} alkoxy, OCF_3, F, Cl, Br, I, $-NR^5R^{5a}$, $-NO_2$, -CN, $-C(O)R^6$, $-NHC(O)R^7$, $-NHC(O)NR^5R^{5a}$, $-NHSO_2R^{10}$, $-SO_2NR^5R^{5a}$, and a 5-6 membered heteroaromatic ring containing 1-4 heteroatoms selected from the group O, N, and S;

alternatively, R^3 and R^{3a} together form $-OCH_2O-$;

R^{3b} is selected from the group H, C_{1-4} alkyl, -OH, C_{1-4} alkoxy, OCF_3, F, Cl, Br, I, $-NR^5R^{5a}$, $-NO_2$, -CN, $-C(O)R^6$, $-NHC(O)R^7$, $-NHC(O)NR^5R^{5a}$, $-NHSO_2R^{10}$, and $-SO_2NR^5R^{5a}$;

alternatively, R^{3a} and R^{3b} together form $-OCH_2O-$;

R^{3c} is selected from the group H, C_{1-4} alkyl, -OH, C_{1-4} alkoxy, OCF_3, F, Cl, Br, I, $-NR^5R^{5a}$, $-NO_2$, -CN, $-C(O)R^6$, $-NHC(O)R^7$, $-NHC(O)NR^5R^{5a}$, $-NHSO_2R^{10}$, and $-SO_2NR^5R^{5a}$;

alternatively, R^{3b} and R^{3c} together form $-OCH_2O-$;

R^{3d}, at each occurrence, is independently selected from the group C_{1-4} alkyl, -OH, C_{1-4} alkoxy, OCF_3, F, Cl, Br, I,

$-NR^5R^{5a}$, $-NO_2$, -CN, $-C(O)R^6$, $-NHC(O)R^7$, $-NHC(O)NR^5R^{5a}$, $-NHSO_2R^{10}$, and $-SO_2NR^5R^{5a}$;

R^{3e}, at each occurrence, is independently selected from the group C_{1-4} alkyl, -OH, C_{1-4} alkoxy, OCF_3, F, Cl, Br, I, $-NR^5R^{5a}$, $-NO_2$, -CN, $-C(O)R^6$, $-NHC(O)R^7$, $-NHC(O)NR^5R^{5a}$, $-NHSO_2R^{10}$, and $-SO_2NR^5R^{5a}$;

R^{3f}, at each occurrence, is independently selected from the group C_{1-4} alkyl, -OH, C_{1-4} alkoxy, OCF_3, F, Cl, Br, I, $-NR^5R^{5a}$, $-NO_2$, -CN, $-C(O)R^6$, $-NHC(O)R^7$, $-NHC(O)NR^5R^{5a}$, $-NHSO_2R^{10}$, and $-SO_2NR^5R^{5a}$;

R^{3g}, at each occurrence, is independently selected from the group C_{1-4} alkyl, -OH, C_{1-4} alkoxy, OCF_3, F, Cl, Br, I, $-NR^5R^{5a}$, $-NO_2$, -CN, $-C(O)R^6$, $-NHC(O)R^7$, $-NHC(O)NR^5R^{5a}$, $-NHSO_2R^{10}$, $-SO_2NR^5R^{5a}$, C_{3-10} carbocycle substituted with 0-3 R^{3f} and a 5-10 membered heterocyclic group containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-3 R^{3f}; and,

R^4 is selected from the group F, Cl, Br, I, C_{1-6} alkyl substituted with 0-2 R^{3e}, C_{3-10} carbocycle substituted with 0-2 R^{3e}, phenyl substituted with 0-5 R^{3e}, and a 5-10 membered heterocyclic group containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^{3e};

R^5 and R^{5a} are independently selected from the group H and C_{1-4} alkyl;

alternatively, R^5 and R^{5a}, together with the nitrogen to which they are attached, combine to form a 5-6 membered ring containing 0-1 O or N atoms;

R^6 is selected from the group H, OH, C_{1-4} alkyl, C_{1-4} alkoxy, and NR^5R^{5a};

R^7 is selected from the group C_{1-3} alkyl and C_{1-3} alkoxy;

R^8 is selected from the group H, OR^9, SR^9, NR^5R^9, C_{1-6} alkyl substituted with 0-3 R^{3g}, C_{2-6} alkenyl substituted with 0-3 R^{3g}, C_{2-6} alkynyl substituted with 0-3 R^{3g}, C_{3-5} cycloalkyl substituted with 0-2 R^{3f}, phenyl substituted with 0-5 R^{3f}, and a 5-6 membered heterocyclic group containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^{3f};

R^9 is selected from the group C_{3-10} carbocycle substituted with 0-5 R^{3f} and a 5-10 membered heterocyclic group containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^{3f}; and,

R^{10} is selected from the group C_{1-4} alkyl and phenyl.

[2] In a preferred embodiment, the present invention provides a novel compound of formula I, wherein:

B is NR^8;

R^1 is selected from the group C_{1-3} alkyl substituted with 1-7 halogen and cyclopropyl;

R^2 is selected from the group $-R^{2c}$, $-OR^{2c}$, $-OCHR^{2a}R^{2b}$, $-OCH_2CHR^{2a}R^{2b}$, $-O(CH_2)_2CHR^{2a}R^{2b}$, $-OCHR^{2a}C=C-R^{2b}$, $-OCHR^{2a}C=R^{2c}$, $-OCHR^{2a}C\equiv C-R^{2b}$, $-SR^{2c}$, $-SCHR^{2a}R^{2b}$, $-SCH_2CHR^{2a}R^{2b}$, $-S(CH_2)_2CHR^{2a}R^{2b}$, $-SCHR^{2a}C=C-R^{2b}$, $-SCHR^{2a}C=R^{2c}$, and $-SCHR^{2a}C\equiv C-R^{2b}$;

R^{2a} is selected from the group H, CH_3, CH_2CH_3, $CH(CH_3)_2$, and $CH_2CH_2CH_3$;

R^{2b} is H or R^{2c};

R^{2c} is selected from the group C_{1-5} alkyl substituted with 0-2 R^4, C_{2-5} alkenyl substituted with 0-2 R^4, C_{2-5} alkynyl substituted with 0-1 R^4, C_{3-6} cycloalkyl substituted with 0-2 R^{3d}, and phenyl substituted with 0-2 R^{3d};

R^3, at each occurrence, is independently selected from the group H, C_{1-4} alkyl, OH, C_{1-4} alkoxy, F, Cl, Br, I, NR^5R^{5a}, NO_2, -CN, $C(O)R^6$, $NHC(O)R^7$, $NHC(O)NR^5R^{5a}$, and a 5-6 membered heteroaromatic ring containing 1-4 heteroatoms selected from the group O, N, and S;

R^{3a}, at each occurrence, is independently selected from the group H, C_{1-4} alkyl, OH, C_{1-4} alkoxy, F, Cl, Br, I, NR^5R^{5a}, NO_2, -CN, $C(O)R^6$, $NHC(O)R^7$, $NHC(O)NR^5R^{5a}$, and a 5-6 membered heteroaromatic ring containing 1-4 heteroatoms selected from the group O, N, and S;

alternatively, R^3 and R^{3a} together form $-OCH_2O-$;

R^{3b}, at each occurrence, is independently selected from the group H, C_{1-4} alkyl, OH, C_{1-4} alkoxy, F, Cl, Br, I, NR^5R^{5a}, NO_2, -CN, $C(O)R^6$, $NHC(O)R^7$, and $NHC(O)NR^5R^{5a}$;

alternatively, R^{3a} and R^{3b} together form $-OCH_2O-$;

R^4 is selected from the group Cl, F, C_{1-4} alkyl substituted with 0-2 R^{3e}, C_{3-5} carbocycle substituted with 0-2 R^{3e}, phenyl substituted with 0-5 R^{3e}, and a 5-6 membered heterocyclic group containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^{3e};

R^5 and R^{5a} are independently selected from the group H, CH_3 and C_2H_5;

R^6 is selected from the group H, OH, CH_3, C_2H_5, OCH_3, OC_2H_5, and NR^5R^{5a};

R^7 is selected from the group CH_3, C_2H_5, $CH(CH_3)_2$, OCH_3, OC_2H_5, and $OCH(CH_3)_2$; and,

R^8 is selected from the group H, cyclopropyl, CH_3, C_2H_5, and $CH(CH_3)_2$.

[3] In a more preferred embodiment, the present invention provides a novel compound of formula I, wherein:

R^1 is selected from the group CF_3, C_2F_5, and cyclopropyl;

R^2 is selected from the group $-R^{2c}$, $-OR^{2c}$, $-OCHR^{2a}R^{2b}$, $-OCH_2CHR^{2a}R^{2b}$, $-OCHR^{2a}C=C-R^{2b}$, $-OCHR^{2a}C=R^{2c}$,

$-OCHR^{2a}C\equiv C-R^{2b}$, $-SR^{2c}$, $-SCHR^{2a}R^{2b}$, $-SCH_2CHR^{2a}R^{2b}$, $-SCHR^{2a}C=C-R^{2b}$, $-SCHR^{2a}C=R^{2c}$, and $-SCHR^{2a}C\equiv C-R^{2b}$;

R^{2a} is selected from the group H, CH_3, CH_2CH_3, $CH(CH_3)_2$, and $CH_2CH_2CH_3$;

R^{2b} is H or R^{2c};

R^{2c} is selected from the group C_{1-3} alkyl substituted with 0-2 R^4, C_{2-3} alkenyl substituted with 0-2 R^4, C_{2-3} alkynyl substituted with 0-1 R^4, and C_{3-6} cycloalkyl substituted with 0-2 R^{3d};

R^3, at each occurrence, is independently selected from the group H, C_{1-3} alkyl, OH, C_{1-3} alkoxy, F, Cl, Br, I, NR^5R^{5a}, NO_2, -CN, $C(O)R^6$, $NHC(O)R^7$, and $NHC(O)NR^5R^{5a}$;

alternatively, R^3 and R^{3a} together form $-OCH_2O-$;

R^{3b} is H;

R^{3c} is H;

R^{3e}, at each occurrence, is independently selected from the group H, C_{1-4} alkyl, -OH, C_{1-4} alkoxy, OCF_3, F, Cl, $-NR^5R^{5a}$, $-C(O)R^6$, and $-SO_2NR^5R^{5a}$;

R^4 is selected from the group Cl, F, C_{1-4} alkyl substituted with 0-1 R^{3e}, C_{3-5} carbocycle substituted with 0-2 R^{3e}, phenyl substituted with 0-2 R^{3e}, and a 5-6 membered heterocyclic group containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-1 R^{3e};

R^5 and R^{5a} are independently selected from the group H, CH_3 and C_2H_5;

R^6 is selected from the group H, OH, CH_3, C_2H_5, OCH_3, OC_2H_5, and NR^5R^{5a};

R^7 is selected from the group CH_3, C_2H_5, OCH_3, and OC_2H_5; and,

R^8 is selected from the group H, cyclopropyl, CH_3, and C_2H_5.

[4] In an even more preferred embodiment, the present invention provides a novel compound of formula I, wherein:

R^1 is CF_3;

R^2 is selected from the group $-R^{2c}$, $-OR^{2c}$, $-OCH_2R^{2b}$, $-OCH_2CH_2R^{2b}$, $-OCH_2C{=}C-R^{2b}$, $-OCH_2C{\equiv}C-R^{2b}$, $-SR^{2c}$, $-SCH_2R^{2b}$, $-SCH_2CH_2R^{2b}$, $-SCH_2C{=}C-R^{2b}$, and $-SCH_2C{\equiv}C-R^{2b}$;

R^{2b} is H or R^{2c};

R^{2c} is selected from the group methyl substituted with 0-2 R^4, ethyl substituted with 0-2 R^4, propyl substituted with 0-2 R^4, ethenyl substituted with 0-2 R^4, 1-propenyl substituted with 0-2 R^4, 2-propenyl substituted with 0-2 R^4, ethynyl substituted with 0-2 R^4, 1-propynyl substituted with 0-2 R^4, 2-propynyl substituted with 0-2 R^4, and cyclopropyl substituted with 0-1 R^{3d};

R^3, at each occurrence, is independently selected from the group C_{1-3} alkyl, OH, C_{1-3} alkoxy, F, Cl, NR^5R^{5a}, NO_2, -CN, and $C(O)R^6$;

alternatively, R^3 and R^{3a} together form $-OCH_2O-$;

R^{3d}, at each occurrence, is independently selected from the group CH_3, -OH, OCH_3, OCF_3, F, Cl, and $-NR^5R^{5a}$;

R^{3e}, at each occurrence, is independently selected from the group CH_3, -OH, OCH_3, OCF_3, F, Cl, and $-NR^5R^{5a}$;

R^4 is selected from the group Cl, F, CH_3, CH_2CH_3, cyclopropyl substituted with 0-1 R^{3e}, 1-methyl-cyclopropyl substituted with 0-1 R^{3e}, cyclobutyl substituted with 0-1 R^{3e}, phenyl substituted with 0-2 R^{3e}, and a 5-6 membered heterocyclic group containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-1 R^{3e}, wherein the heterocyclic group is selected from the group 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-oxazolyl, 2-thiazolyl, 4-isoxazolyl, and 2-imidazolyl;

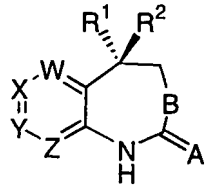
R^5 and R^{5a} are independently selected from the group H, CH_3 and C_2H_5;

R^6 is selected from the group H, OH, CH_3, C_2H_5, OCH_3, OC_2H_5, and NR^5R^{5a};

R^7 is selected from the group CH_3, C_2H_5, OCH_3, and OC_2H_5; and,

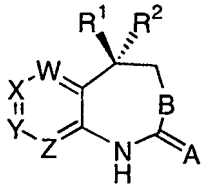
R^8 is selected from the group H, cyclopropyl, and C_2H_5.

[5] In a further preferred embodiment, wherein the compound is of formula Ia



Ia.

[6] In a further preferred embodiment, wherein the compound is of formula Ib:



Ib.

[7] In a further preferred embodiment, the compound of formula I is selected from the group:

7-Chloro-5-(2-cyclopropylethynyl)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

6,7-difluoro-5-(2-cyclopropylethynyl)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-5-(2-cyclopropylethenyl)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-5-(2-cyclopropylethynyl)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-thione;

7-Chloro-5-(2-n-butyl)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-5-(2-cyclopropylethynyl)-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-5-(2-cyclopropylethynyl)-1,5-dihydro-3-ethyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-5-(2-cyclopropylethynyl)-1,5-dihydro-3-cyclopropyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-5-cyclopropylmethyloxy-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-5-(3-methyl-2-butenyloxy)-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-5-(3-allyloxy)-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-5-(3,3-dichloro-2-propenyloxy)-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-5-(2-propynyloxy)-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-5-(2-fluoro-6-methoxybenzyloxy)-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-5-(cyclopropylmethyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-(cyclopropylmethyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-3-cyclopropyl-5-(cyclopropylmethoxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-3-cyclopropyl-5-(cyclopropylmethoxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-3-cyclopropyl-5-propyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-3-cyclopropyl-5-propylthio-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-3-cyclopropyl-5-allylthio-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-3-cyclopropyl-5-allyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-3-cyclopropyl-5-(3-methyl-2-butenyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-3-cyclopropyl-5-cyclobutylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-3-cyclopropyl-5-(1-methylcyclopropyl)methyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-3-cyclopropyl-5-(2-pyridyl)methyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-3-isopropyl-5-cyclopropylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-3-cyclobutyl-5-cyclopropylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-5-(cyclopropylmethoxy)-1,5-dihydro-3-ethyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-(cyclopropylmethyloxy)-1,5-dihydro-3-ethyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-3-ethyl-5-(3-methyl-2-butenyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-3-ethyl-5-allylthio-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-3-ethyl-5-cyclobutylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-3-ethyl-5-cyclopropylmethylthio-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-3-ethyl-5-(1-methylcyclopropyl)methyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-3-propyl-5-cyclopropylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Fluoro-5-(cyclopropylmethoxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Fluoro-3-ethyl-5-cyclopropylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Fluoro-5-(cyclobutylmethoxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Fluoro-3-ethyl-5-cyclobutylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-5-[2-(1-methylcyclopropyl)ethynyl]-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-5-cyclobutylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-5-(3-methyl-2-butenyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-5-(phenylmethyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-5-[(2-pyridyl)methyloxy]-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-5-[(1-methylcyclopropyl)methyoxy]-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-5-(3-methylphenyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-5-(cyclopropylmethylthio)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-5-(propylthio)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one; and,

7-Chloro-5-(2-propenylthio)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

or a pharmaceutically acceptable salt form thereof.

[8] In another further preferred embodiment, the compound of formula I is selected from the group:

(S)-7-Chloro-5-(2-cyclopropylethynyl)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-6,7-difluoro-5-(2-cyclopropylethynyl)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-(2-cyclopropylethenyl)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-(2-cyclopropylethynyl)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-thione;

(S)-7-Chloro-5-(2-n-butyl)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-(2-cyclopropylethynyl)-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-(2-cyclopropylethynyl)-1,5-dihydro-3-ethyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-(2-cyclopropylethynyl)-1,5-dihydro-3-cyclopropyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-cyclopropylmethyloxy-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-(3-methyl-2-butenyloxy)-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-(3-allyloxy)-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-(3,3-dichloro-2-propenyloxy)-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-(2-propynyloxy)-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-(2-fluoro-6-methoxybenzyloxy)-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-(cyclopropylmethyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-(cyclopropylmethyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-3-cyclopropyl-5-(cyclopropylmethoxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-3-cyclopropyl-5-(cyclopropylmethoxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-3-cyclopropyl-5-propyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-3-cyclopropyl-5-propylthio-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-3-cyclopropyl-5-allylthio-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-3-cyclopropyl-5-allyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-3-cyclopropyl-5-(3-methyl-2-butenyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-3-cyclopropyl-5-cyclobutylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-3-cyclopropyl-5-(1-methylcyclopropyl)methyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-3-cyclopropyl-5-(2-pyridyl)methyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-3-isopropyl-5-cyclopropylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-3-cyclobutyl-5-cyclopropylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-(cyclopropylmethoxy)-1,5-dihydro-3-ethyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-(cyclopropylmethyloxy)-1,5-dihydro-3-ethyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-3-ethyl-5-(3-methyl-2-butenyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-3-ethyl-5-allylthio-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-3-ethyl-5-cyclobutylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-3-ethyl-5-cyclopropylmethylthio-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-3-ethyl-5-(1-methylcyclopropyl)methyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-3-propyl-5-cyclopropylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Fluoro-5-(cyclopropylmethoxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Fluoro-3-ethyl-5-cyclopropylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Fluoro-5-(cyclobutylmethoxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Fluoro-3-ethyl-5-cyclobutylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-[2-(1-methylcyclopropyl)ethynyl]-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-cyclobutylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-(3-methyl-2-butenyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-(phenylmethyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-[(2-pyridyl)methyloxy]-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-[(1-methylcyclopropyl)methyoxy]-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-(3-methylphenyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-(cyclopropylmethylthio)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-(propylthio)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one; and,

(S)-7-Chloro-5-(2-propenylthio)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

or a pharmaceutically acceptable salt form thereof.

[9] In another further preferred embodiment, the compound of formula I is selected from the group:

(R)-7-Chloro-5-(2-cyclopropylethynyl)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-6,7-difluoro-5-(2-cyclopropylethynyl)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-(2-cyclopropylethenyl)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-(2-cyclopropylethynyl)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-thione;

(R)-7-Chloro-5-(2-n-butyl)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-(2-cyclopropylethynyl)-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-(2-cyclopropylethynyl)-1,5-dihydro-3-ethyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-(2-cyclopropylethynyl)-1,5-dihydro-3-cyclopropyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-cyclopropylmethyloxy-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-(3-methyl-2-butenyloxy)-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-(3-allyloxy)-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-(3,3-dichloro-2-propenyloxy)-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-(2-propynyloxy)-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-(2-fluoro-6-methoxybenzyloxy)-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-(cyclopropylmethyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-(cyclopropylmethyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-3-cyclopropyl-5-(cyclopropylmethoxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-3-cyclopropyl-5-(cyclopropylmethoxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-3-cyclopropyl-5-propyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-3-cyclopropyl-5-propylthio-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-3-cyclopropyl-5-allylthio-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-3-cyclopropyl-5-allyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-3-cyclopropyl-5-(3-methyl-2-butenyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-3-cyclopropyl-5-cyclobutylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-3-cyclopropyl-5-(1-methylcyclopropyl)methyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-3-cyclopropyl-5-(2-pyridyl)methyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-3-isopropyl-5-cyclopropylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-3-cyclobutyl-5-cyclopropylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-(cyclopropylmethoxy)-1,5-dihydro-3-ethyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-(cyclopropylmethyloxy)-1,5-dihydro-3-ethyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-3-ethyl-5-(3-methyl-2-butenyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-3-ethyl-5-allylthio-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-3-ethyl-5-cyclobutylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-3-ethyl-5-cyclopropylmethylthio-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-3-ethyl-5-(1-methylcyclopropyl)methyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-3-propyl-5-cyclopropylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Fluoro-5-(cyclopropylmethoxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Fluoro-3-ethyl-5-cyclopropylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Fluoro-5-(cyclobutylmethoxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Fluoro-3-ethyl-5-cyclobutylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-[2-(1-methylcyclopropyl)ethynyl]-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-cyclobutylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-(3-methyl-2-butenyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-(phenylmethyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-[(2-pyridyl)methyloxy]-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-[(1-methylcyclopropyl)methyoxy]-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-(3-methylphenyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-(cyclopropylmethylthio)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-(propylthio)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one; and,

(R)-7-Chloro-5-(2-propenylthio)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

or a pharmaceutically acceptable salt form thereof.

In another embodiment, the present invention provides a novel pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of formula I or pharmaceutically acceptable salt form thereof.

In another embodiment, the present invention provides a novel method of treating HIV infection which comprises

administering to a host in need of such treatment a therapeutically effective amount of a compound of formula I or pharmaceutically acceptable salt form thereof.

In another embodiment, the present invention provides a novel method of treating HIV infection which comprises administering, in combination, to a host in need thereof a therapeutically effective amount of:

(a) a compound of formula I; and,

(b) at least one compound selected from the group consisting of HIV reverse transcriptase inhibitors and HIV protease inhibitors.

In another preferred embodiment, the reverse transcriptase inhibitor is selected from the group AZT, ddC, ddI, d4T, 3TC, DPC082, DPC083, DPC961, DPC963, AG1549 delavirdine, efavirenz, nevirapine, Ro 18,893, trovirdine, MKC-442, HBY 097, ACT, UC-781, UC-782, RD4-2025, and MEN 10979, and the protease inhibitor is selected from the group saquinavir, ritonavir, indinavir, amprenavir, nelfinavir, palinavir, BMS-232623, GS3333, KNI-413, KNI-272, LG-71350, CGP-61755, PD 173606, PD 177298, PD 178390, PD 178392, U-140690, and ABT-378.

In an even more preferred embodiment, the reverse transcriptase inhibitor is selected from the group AZT, efavirenz, and 3TC and the protease inhibitor is selected from the group saquinavir, ritonavir, nelfinavir, and indinavir.

In a still further preferred ebodiment, the reverse transcriptase inhibitor is AZT.

In another still further preferred embodiment, the protease inhibitor is indinavir.

In another embodiment, the present invention provides a pharmaceutical kit useful for the treatment of HIV infection, which comprises a therapeutically effective amount of:

(a) a compound of formula I or a pharmaceutically acceptable salt form thereof; and,

(b) at least one compound selected from the group consisting of HIV reverse transcriptase inhibitors and HIV protease inhibitors, in one or more sterile containers.

In another embodiment, the present invention provides novel compounds of formula I or pharmaceutically acceptable salt forms thereof for use in therapy.

In another embodiment, the present invention provides the use of novel compounds of formula I or pharmaceutically acceptable salt forms thereof for the manufacture of a medicament for the treatment of HIV.

DEFINITIONS

The compounds herein described may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. Geometric isomers of double bonds such as olefins and C=N double bonds can also be present in the

compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated. All processes used to prepare compounds of the present invention and intermediates made therein are considered to be part of the present invention.

The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced. Keto substituents are not present on aromatic moieties. When a ring system (e.g., carbocyclic or heterocyclic) is said to be substituted with a carbonyl group or a double bond, it is intended that the carbonyl group or double bond be part (i.e., within) of the ring.

The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include C-13 and C-14.

When any variable (e.g., R^6) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R^6, then said group may optionally be substituted with up to two R^6 groups and R^6 at each occurrence is selected independently from the definition of

R^6. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

As used herein, "alkyl" or "alkylene" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. C_{1-6} alkyl (or alkylene), is intended to include C_1, C_2, C_3, C_4, C_5, and C_6 alkyl groups. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, and s-pentyl. "Haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen (for example $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1)). Examples of haloalkyl include, but are not limited to, trifluoromethyl, trichloromethyl, pentafluoroethyl, and pentachloroethyl. "Alkoxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. C_{1-10} alkoxy, is intended to include C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, and C_{10} alkoxy groups. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, n-pentoxy, and s-pentoxy. "Cycloalkyl" is intended to include saturated ring groups, such as cyclopropyl, cyclobutyl, or cyclopentyl. C_{3-10} cycloalkyl, is intended to include C_3, C_4, C_5, C_6, C_7, C_8, C_9, and C_{10}

cycloalkyl groups. "Alkenyl" or "alkenylene" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl and propenyl. C_{2-6} alkenyl (or alkenylene), is intended to include C_2, C_3, C_4, C_5, and C_6 alkenyl groups. "Alkynyl" or "alkynylene" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more triple carbon-carbon bonds which may occur in any stable point along the chain, such as ethynyl and propynyl. C_{2-6} alkynyl (or alkynylene), is intended to include C_2, C_3, C_4, C_5, and C_6 alkynyl groups.

"Halo" or "halogen" as used herein refers to fluoro, chloro, bromo, and iodo; and "counterion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, and sulfate.

As used herein, "carbocycle" or "carbocyclic group" is intended to mean any stable 3, 4, 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, or 10-membered bicyclic or tricyclic, any of which may be saturated, partially unsaturated, or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane, [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, and tetrahydronaphthyl.

As used herein, the term "heterocycle" or "heterocyclic group" is intended to mean a stable 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, or 10-membered bicyclic heterocyclic ring which is saturated, partially unsaturated or unsaturated (aromatic), and which consists of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, NH, O and S and including any bicyclic group in which any of the above-defined

heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized. The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom which results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. A nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1. As used herein, the term "aromatic heterocyclic group" or "heteroaryl" is intended to mean a stable 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, or 10-membered bicyclic heterocyclic aromatic ring which consists of carbon atoms and 1, 2, 3, or 4 heterotams independently selected from the group consisting of N, NH, O and S. It is to be noted that total number of S and O atoms in the aromatic heterocycle is not more than 1.

Examples of heterocycles include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4a*H*-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1*H*-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl,

phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4*H*-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl. Preferred heterocycles include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrrolidinyl, imidazolyl, indolyl, benzimidazolyl, 1*H*-indazolyl, oxazolidinyl, benztriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, and isatinoyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

As used herein, "HIV reverse transcriptase inhibitor" is intended to refer to both nucleoside and non-nucleoside inhibitors of HIV reverse transcriptase (RT). Examples of nucleoside RT inhibitors include, but are not limited to, AZT, ddC, ddI, d4T, and 3TC. Also included is Glaxo's combination of AZT and 3TC. Examples of non-nucleoside RT inhibitors include, but are no limited to, DPC082 (DuPont, (+)-4-Cyclopropylethenyl-5,6-difluoro-4-trifluoromethyl-3,4-dihydro-2(1H)-quinazolinone), DPC083 (DuPont, (-)-6-chloro-4-E-cyclopropylethenyl-4-trifluoromethyl-3,4-dihydro-2(1H)-quinazolinone), DPC961 (DuPont, (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-3,4-dihydro-2(1H)-quinazolinone), DPC963 (DuPont, (+)-4-Cyclopropylethynyl-5,6-difluoro-4-trifluoromethyl-3,4-dihydro-2(1H)-quinazolinone), AG1549 (Warner Lambert/Shionogi),

delavirdine (Pharmacia and Upjohn U90152S), efavirenz (DuPont), nevirapine (Boehringer Ingelheim), Ro 18,893 (Roche), trovirdine (Lilly), MKC-442 (Triangle), HBY 097 (Hoechst), ACT (Korean Research Institute), UC-781 (Rega Institute), UC-782 (Rega Institute), RD4-2025 (Tosoh Co. Ltd.), and MEN 10979 (Menarini Farmaceutici).

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic groups such as amines; and alkali or organic salts of acidic groups such as carboxylic acids. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, and nitric; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, and isethionic.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which

contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (e.g., solubility, bioavailability, manufacturing, etc...) the compounds of the present invention may be delivered in prodrug form. Thus, the present invention is intended to cover prodrugs of the presently claimed compounds, methods of delivering the same and compositions containing the same. "Prodrugs" are intended to include any covalently bonded carriers which release an active parent drug of the present invention *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of the present invention are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Prodrugs include compounds of the present invention wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug of the present invention is administered to a mammalian subject, it cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of the present invention.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive

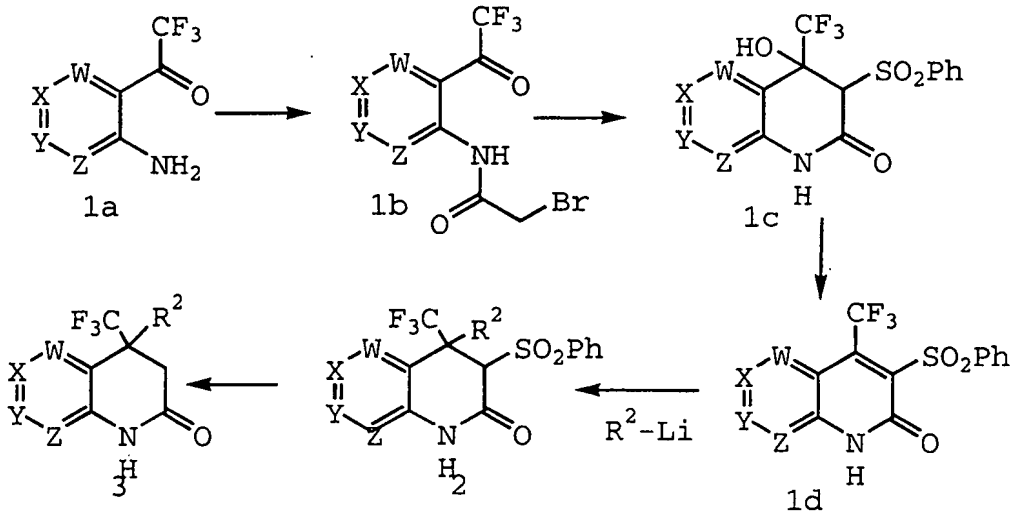
isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

"Therapeutically effective amount" is intended to include an amount of a compound of the present invention or an amount of the combination of compounds claimed effective to inhibit HIV infection or treat the symptoms of HIV infection in a host. The combination of compounds is preferably a synergistic combination. Synergy, as described for example by Chou and Talalay, Adv. Enzyme Regul. 22:27-55 (1984), occurs when the effect (in this case, inhibition of HIV) of the compounds when administered in combination is greater than the additive effect of the compounds when administered alone as a single agent. In general, a synergistic effect is most clearly demonstrated at suboptimal concentrations of the compounds. Synergy can be in terms of lower cytotoxicity, increased antiviral effect, or some other beneficial effect of the combination compared with the individual components.

SYNTHESIS

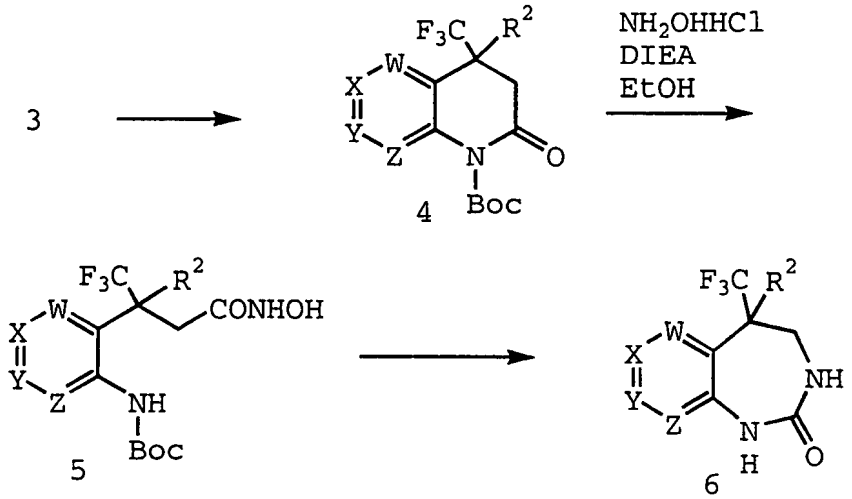
The compounds of the present invention can be prepared in a number of ways well known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Preferred methods include but are not limited to those methods described below. Each of the references cited below are hereby incorporated herein by reference. In the Schemes which follow, R^1 is shown as a CF_3 group, but could be any one of the presently described R^1 groups.

SCHEME 1



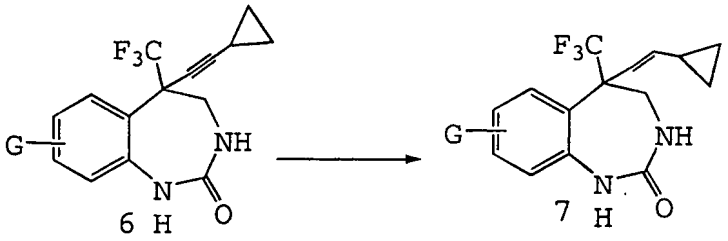
Scheme 1 illustrates a method of making tetrahydroquinolinone intermediates. An appropriately substituted amino-ketone is acylated and the resulting amide cyclized in the presence of benzenesulfinate to give alcohol **1c**. Dehydration with base provides the α,β-unsaturated ketone **1d** which can be modified via a lithium or grignard reagent to give **2**. Sulfone reduction can be achieved with Al/Hg or other known methods of reduction to leave intermediate **3**.

SCHEME 2



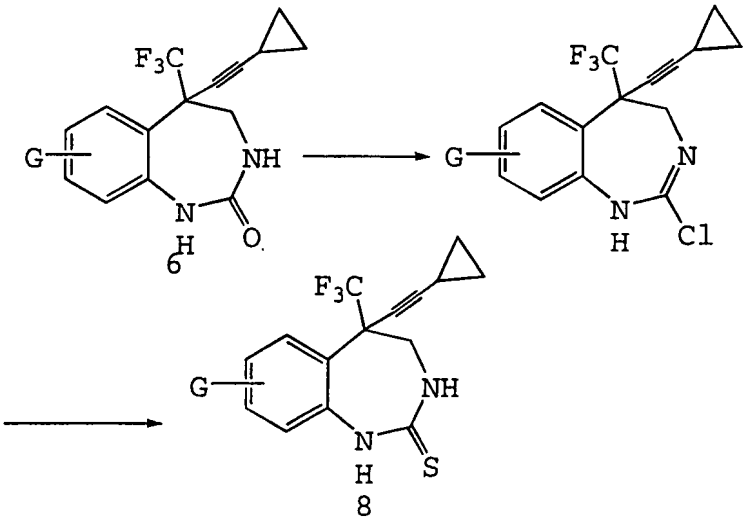
Scheme 2 depicts modification of intermediate **3** into a 1,3-benzodiazepin-2-one. Compound **3** is protected as amide **4** using Boc-anhydride and ring opened to hydroxamide **5**. Lossen rearrangement and deprotection can then be accomplished with tosyl chloride and based followed by trifluoracetic acid to give the desired 1,3-benzodiazepin-2-one **6**.

SCHEME 3



Scheme 3 illustrates a method of reducing acetylene **6** to cis-olefin **7** using NH_2OSO_3H and DIEA. Other methods known to reduce alkynes to alkenes could also be used. In Scheme 3 and the Schemes which follow, G can be R^3, R^4, R^5, R^6 or a combination of two or more of these groups.

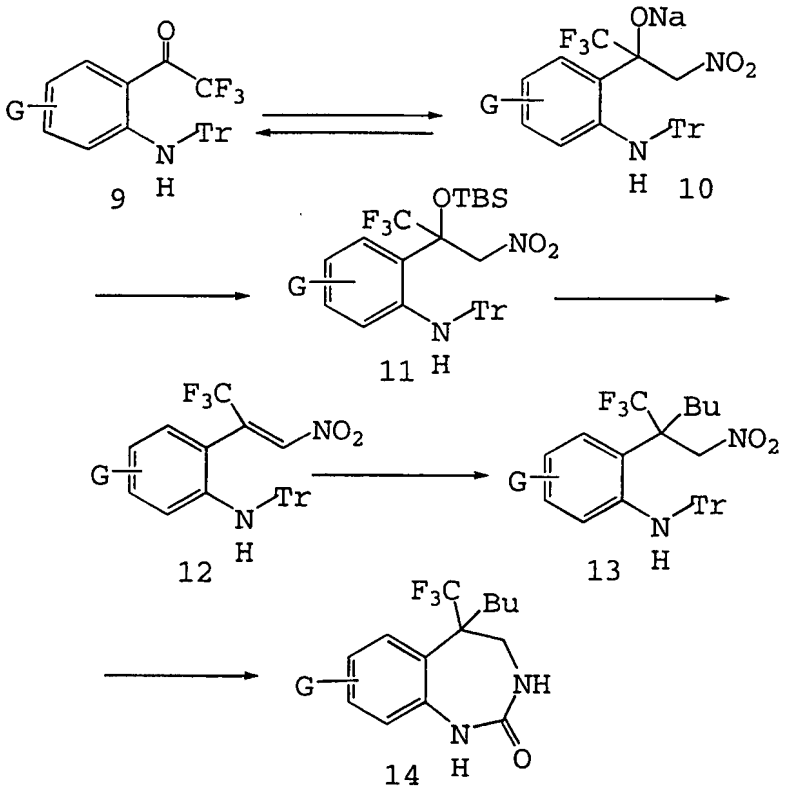
SCHEME 4



Thioureas of the present invention can be formed as shown in Scheme 4 from their corresponding ureas. Urea **6** is initially converted into a halo-imine via a chlorinating agent sucb as $POCL_3$ which is then further transformed into thiourea **8** with $NH_2C(S)NH_2$.

An alternative method of preparing compounds of the present invention is shown below in Scheme 5 and proceeds through a nitro-olefin intermediate.

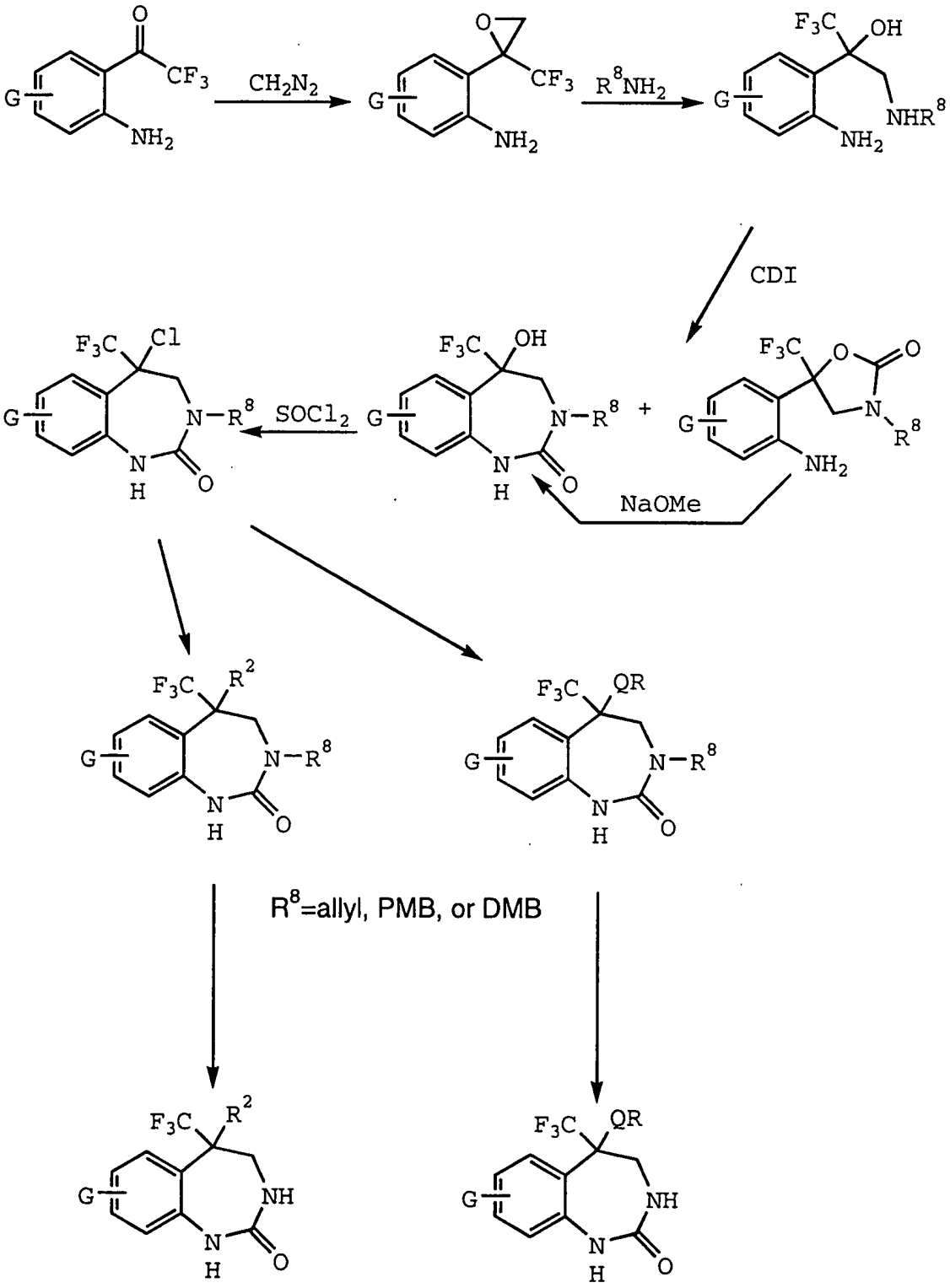
SCHEME 5



Starting from appropriately substituted ketone **9**, nitromethane is added and alkoxide **10** is quenched with a protecting group like TBS-Cl to provide silyl ether **11**. Nitro-olefin **12** can be formed by heating **11** in the presence of a base (e.g., K_2CO_3). R^2 (e.g., butyl) can be attached via grignard addition (e.g., BuMgCl), $(R^2)_3Al$ addition (e.g.,

(cyclopropylethyl)$_3$Al) or other known methods of addition to nitro-olefins. Modification to **14** can be achieved by reduction of the nitro group to an amino group, deprotection of the aniline amine and finally cyclization with a carbonyl reagent like CDI.

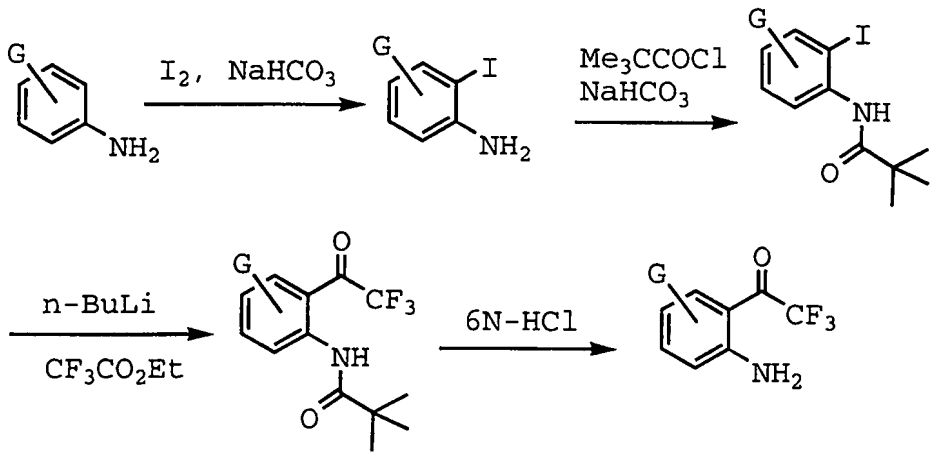
SCHEME 6



An alternate means of preparing compounds of the present invention is presented in Scheme 6. The trifluoromethyl ketone is treated with diazomethane,

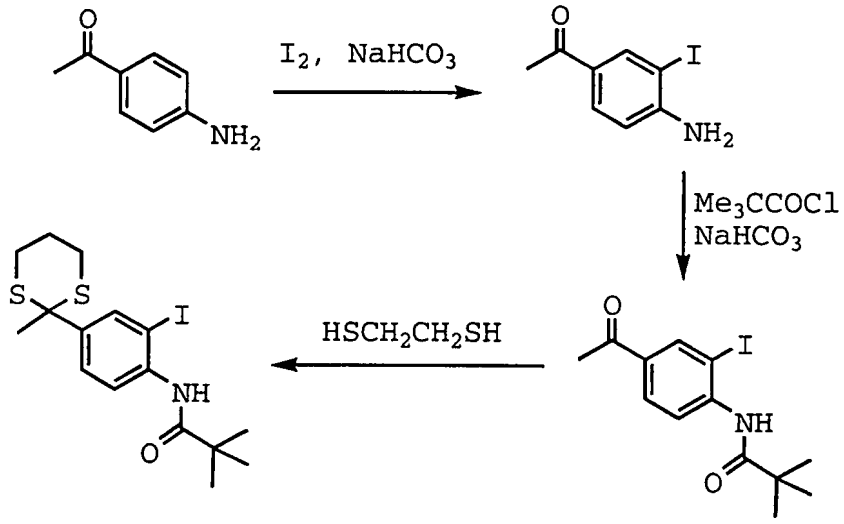
dimethylsulfonium methylide, or dimethylsulfoxonium methylide to give the epoxide. The epoxide is then reacted with a primary amine to give the ring opened alcohol which on treatment with N,N'-carbonyldiimidazole affords a mixture of 5- and 7-membered cyclic amides. Treatment of this mixture with sodium methoxide or triethylamine in ethanol converts it to the desired 7-membered cyclic urea. In addition to N,N'-carbonyldiimidazole, conversion to the cyclic urea can also be accomplished with phosgene, triphosgene, methylchloroformate or a number of similar reagents well-known to practitioners of the art. Treatment of the cyclic urea with thionyl chloride gives the chloride, a compound which when treated with a lithium reagent or a Grignard reagent affords the R^2 substituted compound (R^2 = alkyl, aryl, alkynyl, or alkenyl). Reaction of the chloride with an amine, an alkoxide, or a thioalkoxide gives the QR substituted compound (Q = O, S, NH). For the synthesis of compounds of the invention in which R^8 = H, it is preferred to open the epoxide with an amine ($R^8 NH_2$) whose alkyl group (R^8) can be removed in the final synthetic step. Several such removable alkyl groups are well known to practitioners of the art, preferred examples of which are allyl, p-methoxybenzyl (PMB) and 2,4-dimethoxybenzyl (DMB). The allyl group can be removed by treatment with rhodium chloride followed by aqueous acid. The PMB and DMB groups can be removed by catalytic hydrogenation, treatment with a strong acid such as trifluoroacetic acid, or by treatment with an oxidizing agent such as ceric ammonium nitrate, DDQ, or sodium persulfate.

SCHEME 7



Scheme 7 describes a means of obtaining an amino-ketone useful in the previous schemes. After iodination of an appropriate aniline, the trifluoromethyl group can be introduced using a strong base and ethyl trifluoroacetate.

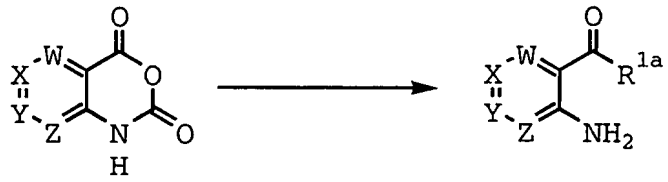
SCHEME 8



Because certain benzo-substituents are incompatible with the methods of the previous schemes, it may be necessary to protect these groups before forming the desired product. In Scheme 8 there is shown a means of obtaining carbonyl-substituted iodo-anilines which can be modified as shown in Scheme 7. After iodination of an acetyl-aniline, the acetyl group is protected by means well known to those

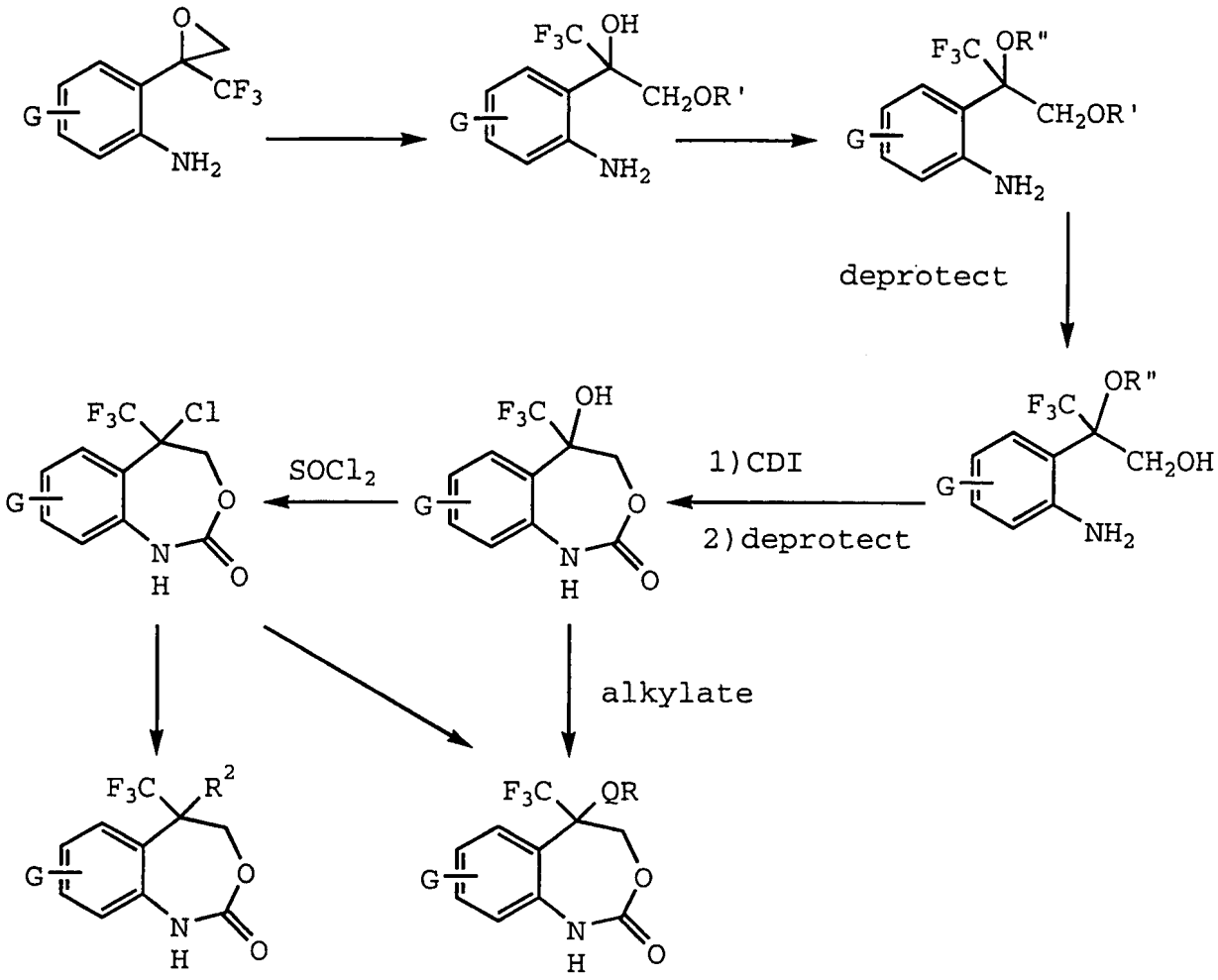
of skill in the art, such as using 1,3-propanedithiol. Deprotection of the ketone can then be achieved using $HgCl_2$ and HgO or other means well known to those of skill in the art.

SCHEME 9



In addition to the methods of obtaining keto-anilines described previously, nucleophilic opening of isatoic anhydrides can also be used as shown in Scheme 9. This reaction is accomplished by using an anionic nucleophile of the group R^{1a}. See Mack et al, *J. Heterocyclic Chem.* **1987**, *24*, 1733-1739; Coppola et al, *J. Org. Chem.* **1976**, *41(6)*, 825-831; Takimoto et al, *Fukuoka Univ. Sci. Reports* **1985**, *15(1)*, 37-38; Kadin et al, *Synthesis* **1977**, 500-501; Staiger et al, *J. Org. Chem.* **1959**, *24*, 1214-1219.

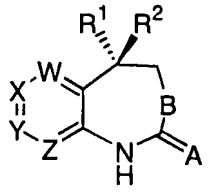
SCHEME 10



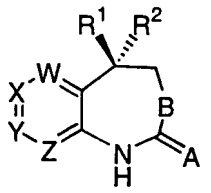
The 1,3-benzoxazepinones of this invention can be synthesized as described in Scheme 10. The starting epoxide can be ring-opened with an alkoxide (NaOR', or KOR') in which R' is a protecting group which can be removed later in the synthesis. There are many such removable groups known to practitioners of the art. These include the allyl group, as well as substituted ethyl groups such as 2-trimethylsilylethyl or 2,2,2-trichloroethyl, or substituted benzyl groups such as 3,4-dimethoxybenzyl, p-nitrobenzyl, and diphenylmethyl. The next step is to protect the tertiary alcohol with a second protecting group (R") which is stable to the conditions for the removal of the first protecting group (R'). This second protecting group can be

one of the allyl, substituted ethyl, or substituted benzyl groups as described above, or it can be a silyl group (such as triethylsilyl, t-butyldimethylsilyl, or t-butyldiphenylsilyl). There are many combinations of two selectively removable protecting groups which are well known to practitioners of the art. Removal of the first protecting group affords the primary alcohol which upon treatment with N,N'-carbonyldiimidazole or phosgene followed by removal of the second protecting group affords the cyclic carbamate. Treatment of the cyclic carbamate with thionyl chloride converts the tertiary alcohol to a chloride. This compound when treated with a lithium reagent or a Grignard reagent affords the R^2 substituted compound (R^2 = alkyl, aryl, alkynyl, or alkenyl). Reaction of the chloride with an amine, an alkoxide, or a thioalkoxide gives the QR substituted compound (Q = O, S, NH). Additionally, compounds of this invention in which Q = O can also be prepared by direct alkylation of the tertiary alcohol.

One enantiomer of a compound of Formula I may display superior activity compared with the other. Thus, the following stereochemistries are considered to be a part of the present invention.



Ia



Ib

When required, separation of the racemic material can be achieved by HPLC using a chiral column as exemplified in Examples 27-34 (Scheme 4) or by a resolution using a resolving agent such as camphonic chloride as in Thomas J. Tucker, et al, *J. Med. Chem.* **1994**, *37*, 2437-2444. A chiral compound of Formula I may also be directly synthesized using a chiral catalyst or a chiral ligand, e.g. Mark A. Huffman, et al, *J. Org. Chem.* **1995**, *60*, 1590-1594.

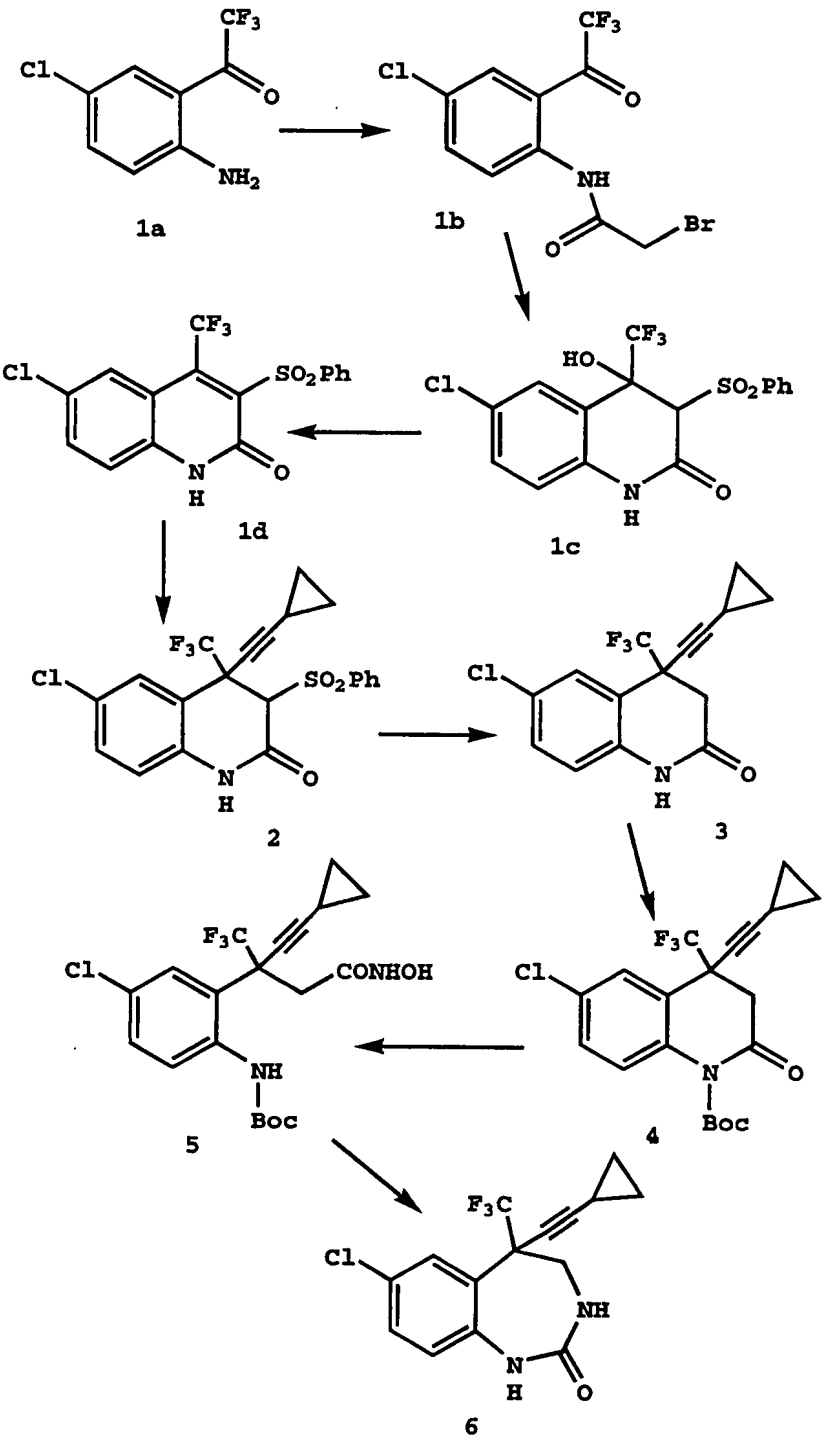
Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments which are given for illustration of the invention and are not intended to be limiting thereof.

EXAMPLES

Abbreviations used in the Examples are defined as follows: "°C" for degrees Celsius, "d" for doublet, "dd" for doublet of doublets, "eq" for equivalent or equivalents, "g" for gram or grams, "mg" for milligram or milligrams, "mL" for milliliter or milliliters, "H" for hydrogen or hydrogens, "hr" for hour or hours, "m" for multiplet, "M" for molar, "min" for minute or minutes, "MHz" for megahertz, "MS" for mass spectroscopy, "nmr" or "NMR" for nuclear magnetic resonance spectroscopy, "t" for triplet, "TLC" for thin layer chromatography, "ACN" for acetic anhydride, "CDI" for carbonyl diimidazole, "DIEA" for diisopropylethylamine, "DIPEA" for diisopropylethylamine, "DMAP" for dimethylaminopyridine, "DME" for dimethoxyethane, "EDAC" for 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, "LAH" for lithium aluminium hydride, "TBAF" for tetrabutylammonium fluoride, "TBS-Cl" for t-butyldimethylsilyl chloride, and "TEA" for triethylamine.

Example 1

Preparation of 7-chloro-5-(2-cyclopropylethynyl)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one



To a solution of amino ketone **1a** (3.02 g, 13.54 mmol) in THF (55 mL) at room temperature was added potassium

carbonate (4.67 g, 33.85 mmol) followed by bromoacetyl bromide (1.5 mL, 16.93 mmol) and the resulting reaction mixture was allowed to stir at room temperature for 3 hours. The reaction mixture was poured onto water and extracted with ethyl acetate (3x100 mL). The combined ethyl acetate extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a yellow oil **1b**. This product was used in the next step of the synthetic sequence without further purification.

To a solution of bromide **1b** (crude product, 13.54 mmol) in DMF (55 mL) at room temperature was added sodium benzenesulfinate (4.44 g, 27.08 mmol) and the resulting reaction mixture was allowed to stir at room temperature for 18 hours. The reaction mixture was poured onto water and extracted with ethyl acetate (3x100 mL). The combined ethyl acetate extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The group is triturated with hexanes (1 L) and dried in vacuo to give 4.88 g an off-white solid **1c** (5.49 g theoretical, 89%). ^1H NMR (300 MHz, DMSO-d_6) δ 11.0(br s , 1H), 7.96(s, 1H), 7.76(d, 2H, J = 8 Hz), 7.66(m, 1H), 7.51(m, 2H), 7.44(s, 1H), 7.33(m, 1H), 6.82(d, 1H, J = 8 Hz), 4.47(s, 1H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -80.99(s, 3F). High resolution mass spec: calculated for $C_{16}H_{11}NO_4F_3ClS(M+H)+$: 405.0042, found 405.0049.

To a slurry of the *tertiary* alcohol **1c** (6.815 g, 16.83 mmol) in methylene chloride (100 mL) at room temperature was added 4-(dimethylamino)pyridine (4.11 g, 33.65 mmol) followed by acetic anhydride (3.5 mL, 37.03 mmol) and the resulting reaction mixture is allowed to stir at room temperature for 18 hours. The reaction mixture was poured onto water and extracted with ethyl acetate (3x100 mL). The ethyl acetate extracts were washed with saturated $NaHCO_3$ and dried over anhydrous Na_2SO_4 and concentrated in vacuo. The group is triturated with hexanes (1 L) and dried in vacuo to give 6.06 g an off-white solid **1d** (93%). Anal.

($C_{16}H_9NO_3F_3ClS$) calcd: C 49.56, H 2.35, N 3.61, Cl 9.14, F 14.70, S 8.28. Found: C 49.26, H 2.68, N 3.30, Cl 9.23, F 14.49, S 8.13.

To a 0°C solution of cyclopropyl acetylene (48% purity, 14.6 mL, 80.9 mmol) in THF (95 mL) was syringed 1.6 M BuLi in hexane (46 mL, 73.5 mmol). After the reaction was stirred for 15-30 min. at 0°C, **1** (9.5 g, 24.5 mmol) was added as a solid and stirred for 2 h. The reaction was quenched with saturated NH_4Cl. The reaction was partitioned between EtOAc and saturated NH_4Cl, washed with brine, dried (Na_2SO_4) and evaporated to give a solid. Flash chromatography (50% EtOAc/hexane) gave a white solid **2** (6.6 g, 60% yield).

A mixture of **2** (6.6g, 14.5 mmol), Al/Hg in THF (90 mL) and water (10 mL) was refluxed for 1 h. The reaction was filtered through celite, partitioned between EtOAc and water, washed with brine, dried (Na_2SO_4) and evaporated to give a solid **3** (4 g, 90% yield). MH^+ = 314.0559.

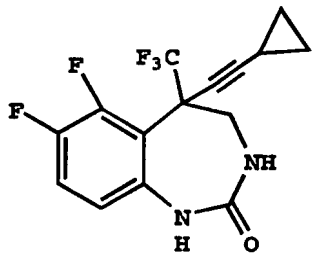
A solution of **3** (4 g, 12.8 mmol), $(Boc)_2O$ (3.06 g 14 mmol) and DMAP (1.56 g, 12.8 mmol) in ACN (60 mL) was stirred for 1 h. TLC indicated that the ratio of the desired product to starting material was about 3 to 2. More $(Boc)_2O$ (0.6 g, 2.8 mmol) was added and the reaction was stirred for 10 min. TLC showed trace of starting material. The reaction was partitioned between EtOAc and 1N HCl, washed with water, saturated $NaHCO_3$ and brine, dried (Na_2SO_4) and evaporated to give an orange solid **4** (4.93 g, 93% yield).

A mixture of **4** (4.63 g, 11.2 mmol), $H_2NOH \cdot HCl$ (3.11 g, 44.8 mmol) and DIEA (7.8 mL, 44.8 mmol) in EtOH (65 mL) was stirred for 2 h. The reaction was diluted with EtOAc, washed with dilute HCl (6X), water, saturated $NaHCO_3$, brine and dried (Na_2SO_4) and evaporated to give a thick orange oil **5** (5.3 g, 95% yield).

A solution of **5** (4.94 g, 11 mmol), TsCl (5.32 g, 27.9 mmo) and 1N NaOH (53.2 mL, 53.2 mmol) in dioxane (240 mL) was stirred for 1.5 h. The reaction was partitioned between EtOAc and saturated $NaHCO_3$, washed with brine, and evaporated to give a semi-solid. A solution of the semi-solid in TFA (20 mL) and CH_2Cl_2 (200 mL) was stirred for 2 h and evaporated to give a thick oil. The oil was partitioned between EtOAc and saturated $NaHCO_3$ and brine, dried (Na_2SO_4) and evaporated to give a thick dark orange oil. Crystallized from dichloroethane to give a white crystalline solid **6** (1.25 g, 40% yield, mp 240-242°C).

Example 2

Preparation of 6,7-difluoro-5-(2-cyclopropylethynyl)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one

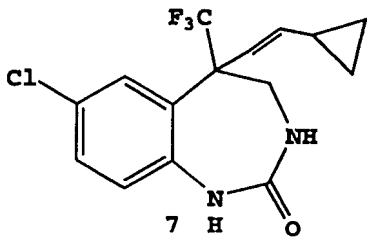


6a

The 6,7-diF analog **6a** was prepared using the same sequence as Example 1, but starting from the difluoro analog **1a**, mp=232-233°C.

Example 3

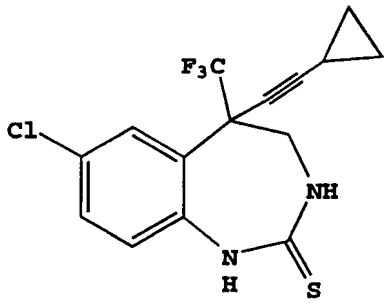
Preparation of 7-chloro-5-(2-cyclopropylethenyl)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one



A suspension of **6** (60 mg), NH_2OSO_3H (1.5 g) and DIEA (3 mL) in THF (5 mL) was refluxed for 48 h. The reaction was diluted with EtOAc, washed with 1 N HCl (2X), water, brine and dried (Na_2SO_4) and evaporated to give a solid which crystallized from dichloroethane to provide a white crystalline solid **7** (30 mg, mp 221-223°C).

Example 4

Preparation of 7-Chloro-5-(2-cyclopropylethynyl)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-thione

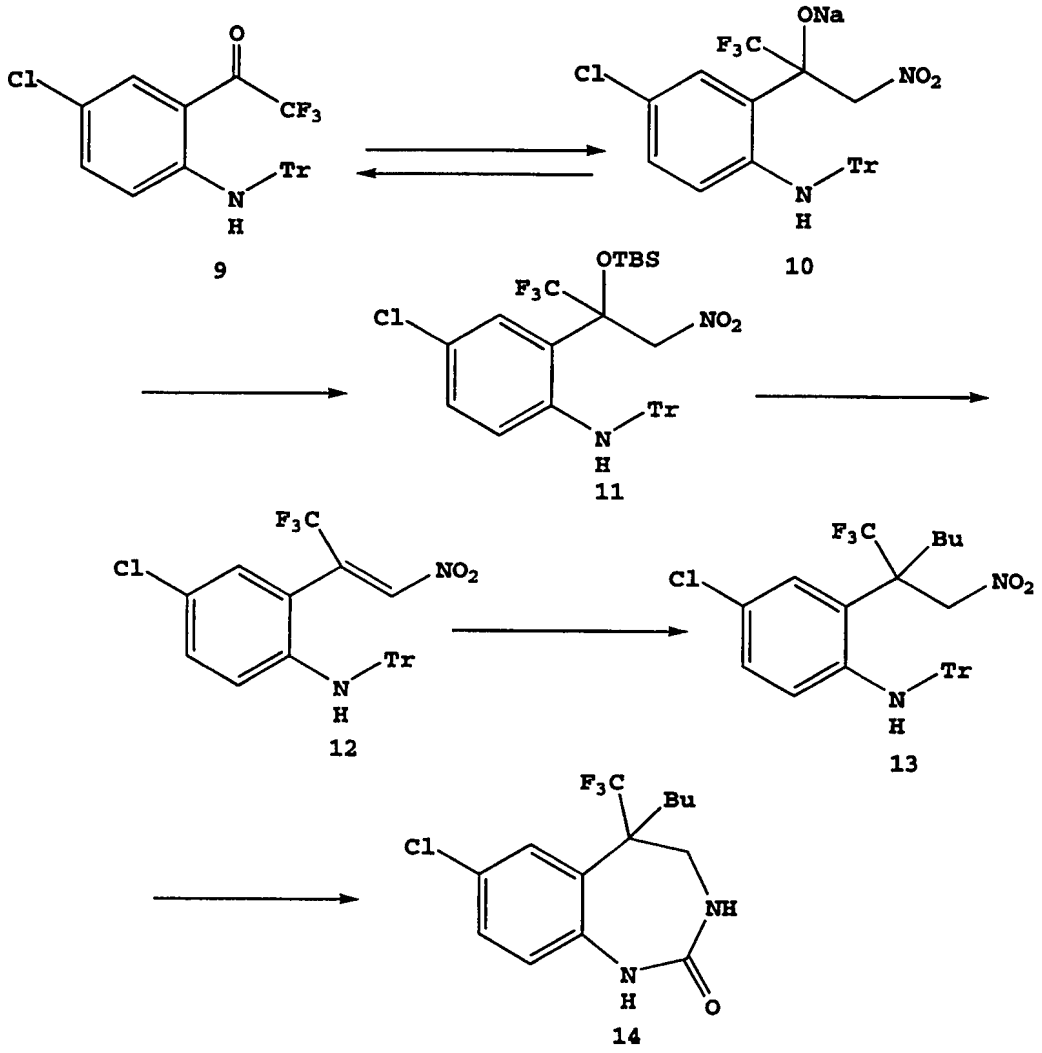


8

A suspension of **6** (50 mg) and Na_2CO_3 (24 mg) in $POCl_3$ (1 mL) was heated at 95°C for 24 h and evaporated to give a semi-solid. The solid and NH_2CSNH_2 (63 mg) in EtOH (4 mL) was refluxed over weekend. The reaction was diluted with EtOAc, washed with water and brine, dried (Na_2SO_4) and evaporated to give a solid. Flash chromatography (25-50% EtOAc/hexane) gave a white solid (22 mg). Crystallized from dichloroethane gave a white crystalline solid **8** (13 mg, mp 230°C dec.).

Example 5

Preparation of 7-Chloro-5-(2-n-butyl)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one



To a solution of **9** (8.48 g, 18.2 mmol) and nitromethane (1.97 mL, 36.4 mmol) in DME (85 mL) was added 60% NaH (2.55 g, 63.8 mmol). After stirring for 1.5 h, TLC indicated that the ratio of the alcohol intermediate **10** to starting material was about 2 to 3. TBS-Cl (13.7 g, 91 mmol) was added and the reaction was stirred for 0.5 h. TLC indicated that the ratio of the desired product **11** to **10** was about 4 to 1. The reaction was stirred for another 2 h. The reaction was diluted with EtOAc and partitioned between EtOAc and saturated $NaHCO_3$. The reaction was filtered and

the organic phase was washed with brine, dried (Na_2SO_4) and evaporated to give an orange oil (22.3 g). The oil was triturated with hexane and washed with same solvent two times to provide a yellow solid **11** (8.2 g, 75% yield).

A mixture of **11** (8.2 g, 13.8 mmol) and K_2CO_3 (2.2 g) in toluene (80 mL) was refluxed for 0.5 h. The reaction was diluted with EtOAc and washed with water and brine, dried (Na_2SO_4) and evaporated to give an dark orange oil (7.4 g). The oil was triturated with hot hexane and washed with same solvent two times to provide a brown solid **12** (5 g, 71.5% yield).

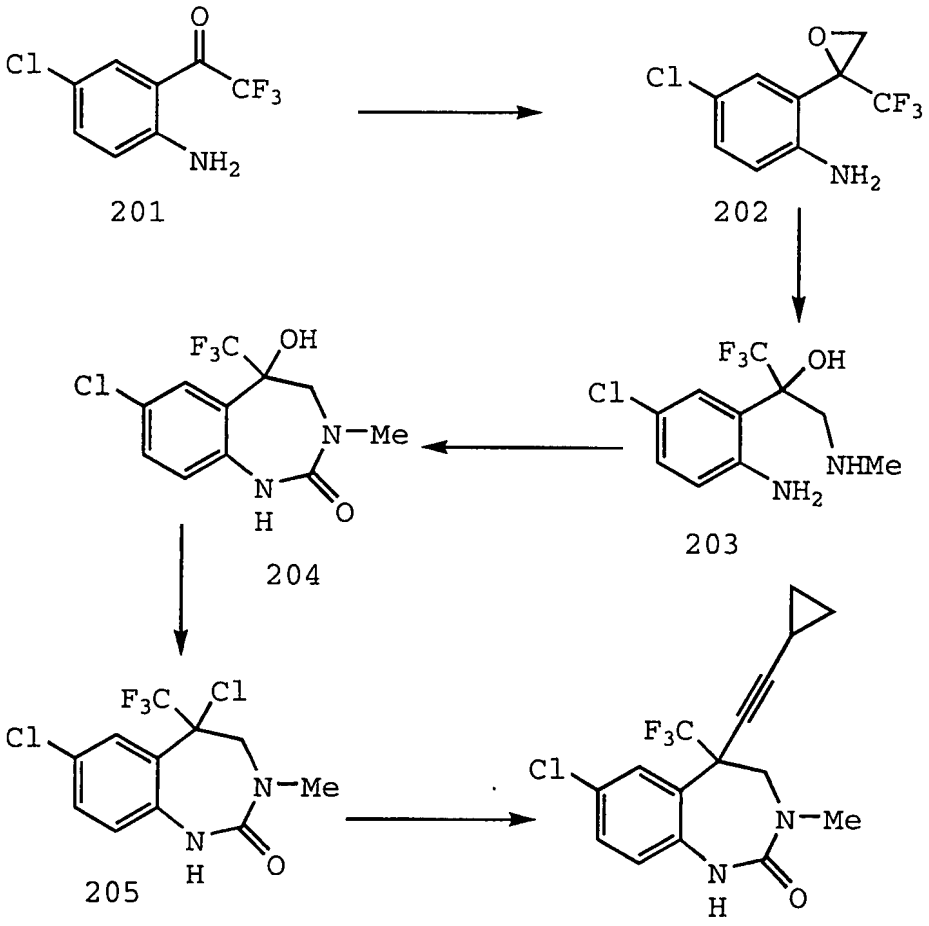
To a -78°C solution of **12** (204 mg, 0.4 mmol) in THF (2 mL) was added 2M BuMgCl in ether (0.6 mL, 1.2 mmol), TLC showed no starting material. The reaction was quenched with saturated NH_4Cl and partitioned between EtOAc and saturated NH_4Cl, washed with brine, dried (Na_2SO_4) and evaporated to give an orange oil (240 mg). Flash chromatography (3% EtOAc/hexane) gave a pale yellow glass **13** (94 mg).

A mixture **13** (75 mg), a slurry of Raney nickel (2 mL) and hydrazine monohydrate (0.1 mL) in ethnol (4 mL) was stirred for 2 h. The reaction was filtered with celite and partitioned between EtOAc and water and brine, dried (Na_2SO_4) and evaporated to give an orange oil (85 mg). Flash chromatography (20% EtOAc/hexane) gave a pale yellow glass (46 mg). A solution of the glass (46 mg) in MeOH (1 mL) and concentrated HCl (0.1 mL) was stirred for 15 min. and filtered off. The filtrate was partitioned between EtOAc and 1N NaOH and brine, dried (Na_2SO_4) and evaporated to give an orange oil (20 mg). A solution of the oil (20 mg) and carbonyl diimidazole (33 mg) in THF (1 mL) was stirred overnight. The solvent was evaporated to give an oil which was triturated with Et_2O/hexane/CH_2Cl_2 to provide a fine powder **14** (5.6 mg, mp 174-176°C).

An alternative means of converting **12** to **13** is as follows. To a -78°C solution of **12** (100 mg, 0.2 mmol) in toluene (2 mL) was added 1M $(i\text{-Bu})_3Al$ in toluene (0.4 mL, 0.4 mmol), TLC showed no starting material. The reaction was quenched with 0.1M HCl and partitioned between EtOAc and 0.1M HCl, washed with brine, dried (Na_2SO_4) and evaporated to give an orange oil **13** (121 mg).

Example 6

Preparation of 7-chloro-5-(2-cyclopropylethynyl)-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one



A solution of approximately 15 mmoles of diazomethane in 40 mL of ether was generated from 5 g of Diazald® following the directions provided by the vender (Aldrich Chemical Company). This solution was added to a solution of

201 (2.6 g, 11.6 mmoles) in 10 mL of ether and the reaction mixture was stirred for 3 hr at room temperature at which time tlc showed complete conversion to epoxide **202**. Excess diazomethane was quenched by the addition of acetic acid, 10 mL of ethanol was added, and the solution was concentrated to a volume of approximately 10 mL on a rotary evaporator. To this solution was added 20 mL of a solution of 33% methylamine in ethanol and the mixture was stirred at room temperature overnight. Evaporation of the solvent under reduced pressure afforded **203** (3.4 g) a semisolid product which was used without purification in the next reaction.

To a solution of **203** (2.9 g, 10.8 mmol) in 50 mL of dry THF was added N,N'-carbonyldiimidazole (2.6 g, 16.2 mmol) and the reaction mixture was stirred for 1.75 h at ambient temperature. An additional 500 mg of N,N'-carbonyldiimidazole was added and the reaction was allowed to procede for an additional 30 min. Sodium methoxide in methanol (10 mL of a 3.24M solution) was added and the mixture was refluxed for 30 min. The cooled mixture was poured onto aqueous ammonium chloride, and this mixture was extracted twice with ethyl acetate. The combined extracts were dried over sodium sulfate and evaporated to an orange oil. Flash chromatography (50-70% EtOAc/hexane) gave after washing with methylene chloride a white solid **204** (1.5 g, 42.5% yield).

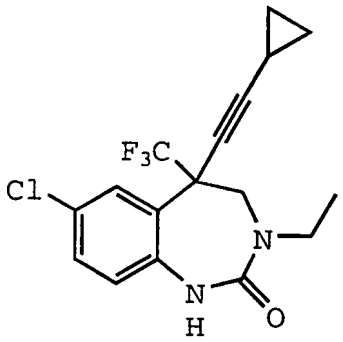
To a solution of **204** (1.17g, 3.97 mmol) in 50 mL of dry THF was added triethylamine (2.3 mL,16.67 mmol) and thionyl chloride (1.2 mL, 15.88 mmol). After stirring 15 min at ambient temperature, 25 mL of methanol was added and this mixture was stirred for 15 min before being poured onto aqueous sodium bicarbonate. The mixture was extracted with ether and the extract was dried over magnesium sulfate and concentrated to a yellow solid **205** (1.18 g, 95% yield) which was used without purification.

To a 0°C solution of cyclopropylacetylene (35% purity, 0.45 mL) in THF (3 mL) was syringed 1.6 M BuLi in hexane

(0.625 mL, 1.0 mmol). After the reaction was stirred for 30 min. at 0°C, the reaction mixture was cooled to -50°C, **205** (85 mg, 0.27 mmol) in THF (0.7 mL) was added and the reaction mixture was allowed to warm to room temperature over 2 h. The reaction was poured onto saturated ammonium chloride and was extracted with ether. The extracts were washed with brine, dried over magnesium sulfate and evaporated to give an oil. Flash chromatography (50% EtOAc/hexane) gave after crystallization from ethyl acetate/hexane colorless crystals of the title compound (27 mg, mp 177-178°C).

Example 7

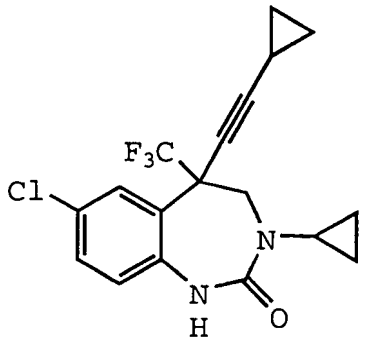
Preparation of 7-chloro-5-(2-cyclopropylethynyl)-1,5-dihydro-3-ethyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one



The title compound (mp 186-188°C) is prepared according to the method of Example 6 by substituting ethylamine for methylamine.

Example 8

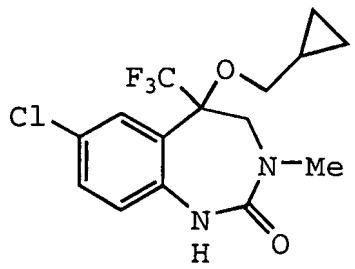
Preparation of 7-chloro-5-(2-cyclopropylethynyl)-1,5-dihydro-3-cyclopropyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one



The title compound (mp 195-196°C) is prepared according to the method of Example 6 by substituting cyclopropylamine for methylamine.

Example 9

Preparation of 7-chloro-5-cyclopropylmethyloxy-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one

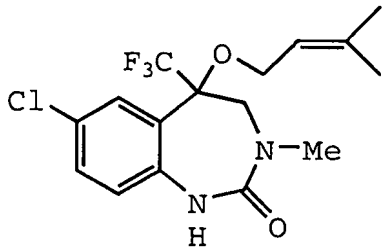


To a solution of cyclopropylcarbinol (250 mg, 3.5 mmol) in 5 mL of dry THF at room temperature was added sodium hydride (50 mg, 2.1 mmol). After 30 min, **205** (150 mg, 0.48 mmol) was added and the reaction mixture was stirred at ambient temperature for 30 min. The reaction was poured onto saturated ammonium chloride and was extracted with ether. The extracts were washed with brine, dried over magnesium sulfate and evaporated to give an oil. Flash chromatography

(50% EtOAc/hexane) gave 49 mg of a solid which was recrystallized from ethyl acetate/hexane to afford colorless crystals of the title compound (20 mg, mp 192-193°C).

Example 10

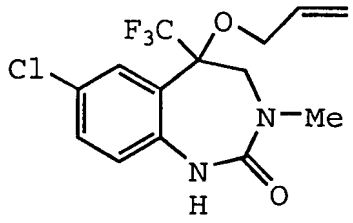
Preparation of 7-chloro-5-(3-methyl-2-butenyloxy)-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one



To a solution of 3-methyl-2-buten-1-ol (310 mg, 3.6 mmol) in 5 mL of dry THF at room temperature was added sodium hydride (80 mg, 3.33 mmol). After 30 min, **205** (160 mg, 0.51 mmol) was added and the reaction mixture was stirred at ambient temperature for 30 min. The reaction was poured onto saturated ammonium chloride and was extracted with ethyl acetate. The extracts were washed with brine, dried over magnesium sulfate and evaporated to give an oil. Flash chromatography (30-50% EtOAc/hexane) gave 90 mg of a solid which was recrystallized from ethyl acetate/hexane to afford colorless crystals of the title compound (mp 181-182°C).

Example 11

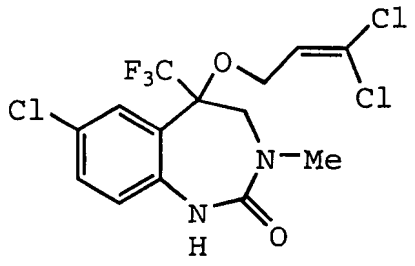
Preparation of 7-chloro-5-(3-allyloxy)-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one



To a solution of allyl alcohol (243 mL, 3.57 mmol) in 5 mL of dry THF at room temperature was added sodium hydride (82 mg, 3.41 mmol). After 30 min, **205** (160 mg, 0.51 mmol) in THF (3 mL) was added and the reaction mixture was stirred at ambient temperature for 35 min. The reaction was poured onto saturated ammonium chloride and was extracted with ethyl acetate. The extracts were washed with brine, dried over magnesium sulfate and evaporated to give an oil. Flash chromatography (40-60% EtOAc/hexane) gave 99 mg of a solid which was recrystallized from ethyl acetate/hexane to afford colorless crystals of the title compound (mp 163-165°C).

Example 12

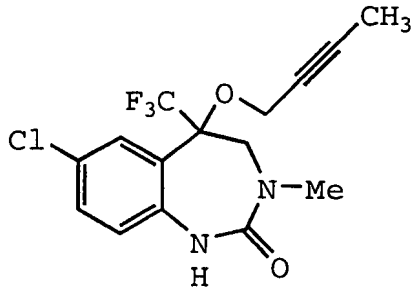
Preparation of 7-chloro-5-(3,3-dichloro-2-propenyloxy)-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one



The title compound (mp 148.6-149.9°C) is prepared according to the method of Example 11 by substituting 3,3-dichloro-2-propenol for allyl alcohol.

Example 13

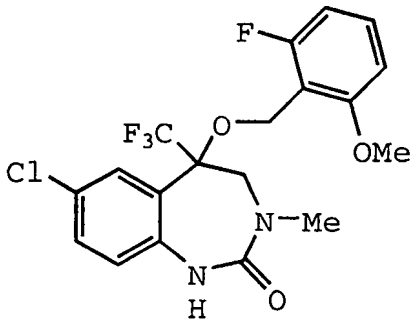
Preparation of 7-chloro-5-(2-propynyloxy)-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one



The title compound (mp 229.7-232.1°C) is prepared according to the method of Example 11 by substituting 2-propyn-1-ol for allyl alcohol.

Example 14

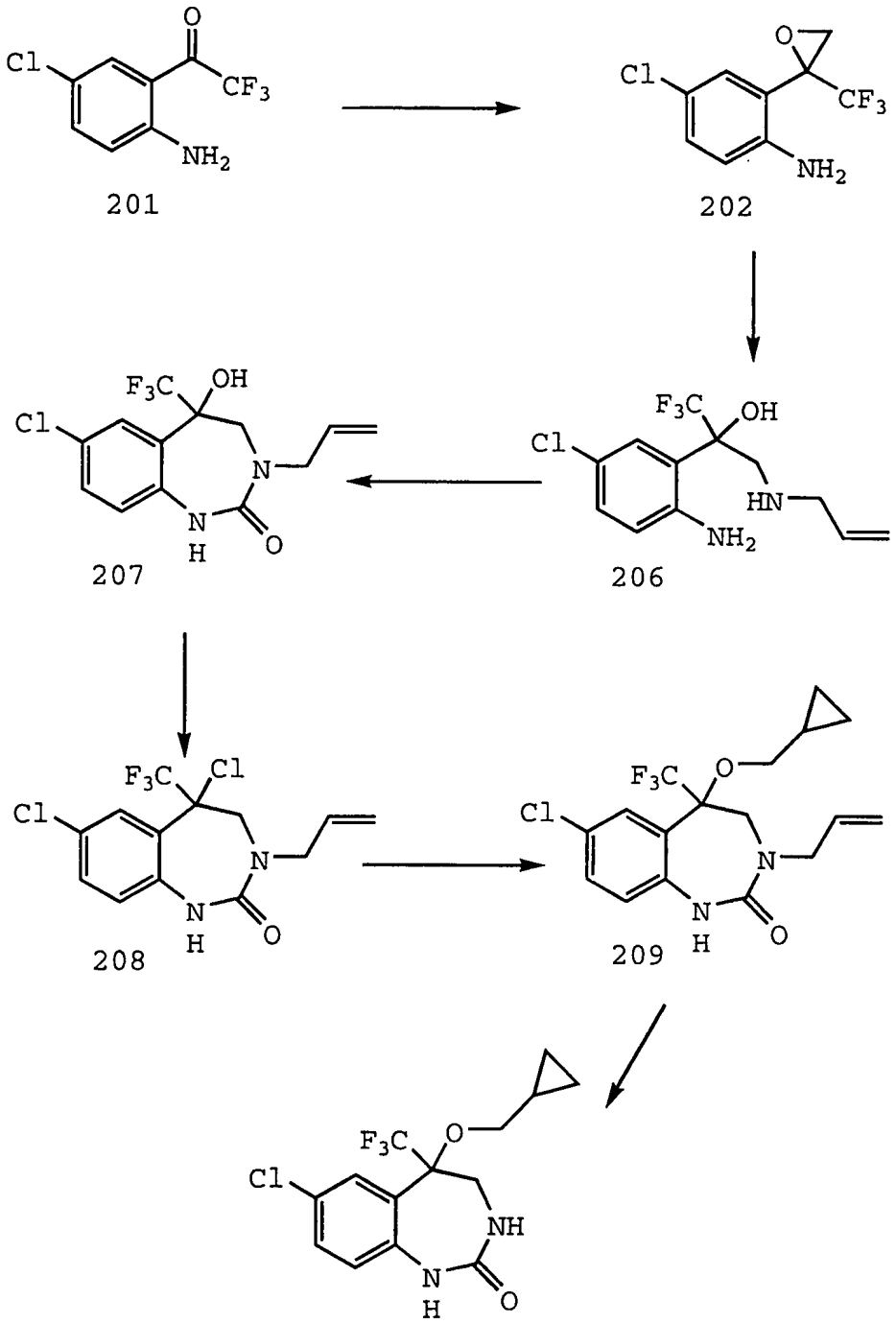
Preparation of 7-chloro-5-(2-fluoro-6-methoxybenzyloxy)-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one



The title compound (mp 172.1-173.8°C) is prepared according to the method of Example 11 by substituting 2-fluoro-6-methoxybenzyl alcohol for allyl alcohol.

Example 15

Preparation of 7-chloro-5-(cyclopropylmethyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one



To a solid mixture of 95% sodium hydride (650 mg, 25.7 mmol) and trimethylsulfoxonium iodide (6.0 g, 27 mmol) was added dropwise with stirring over 15 min, 35 mL of dry DMSO. After an additional 20 min of stirring at ambient

temperature, hydrogen evolution had ceased, and a solution of **201** (3.35 g, 15 mmol) in dry THF (65 mL) was run in over 3 min. After an additional 2 min, the reaction was quenched with water. The reaction mixture was poured onto water and extracted with ether. The ether layer was washed twice with brine and was dried over magnesium sulfate. Ethanol (15 mL) was added to this ethereal solution and this was concentrated at 20° under reduced pressyre to a volume of 15 mL. Allylamine (4.6 g, 81 mmol) was added and the solution was stirred overnight at ambient temperature after which time it was concentrated at 40° to **206** as an oily product.

To a solution of **206** in 65 mL of dry THF was added N,N'-carbonyldiimidazole (2.5 g, 15 mmol) and triethylamine (6.3 mL, 45 mmol) and the reaction mixture was stirred overnight at ambient temperature. Ethanol (25 mL) was added and the mixture was refluxed for 2 h and then evaporated to a small volume. This was taken up in ethyl acetate, and this solution was washed with water, aqueous citric acid, and brine, dried over sodium sulfate and concentrated to an oil. Addition of methylene chloride precipitated the product and **207** was collected as colorless crystals (3.05 g, 63%).

To a solution of **207** (4.6 g, 14.38 mmol) and pyridine (1.393 mL, 17.25 mmol) in 55 mL of dry THF at 0° was added dropwise thionyl chloride (1.865 g, 15.8 mmol). After addition was complete, the cooling bath was removed, and stirring was continued at ambient temperature for 1 h. The reaction mixture was partitioned between water and ethyl acetate, and the organic layer was washed with brine, dried and evaporated to **208** as a crystalline product (4.4 g).

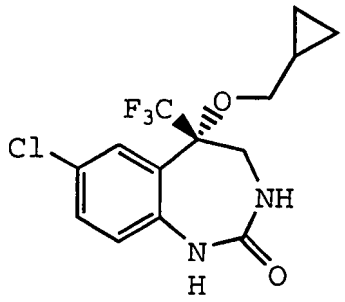
To a solution of cyclopropylmethanol (9 mL) in 45 mL of dry DMSO was added 100% sodium hydride (1.8 g). This was stirred for 3 h at ambient temperature until hydrogen evolution ceased after which time **208** (4.4 g, 13 mmol) was added in one portion. After stirring at ambient temperature for 1 h, the reaction mixture was partitioned between ethyl

acetate and aqueous citric acid, and the organic layer was washed with brine, dried (sodium sulfate) and evaporated to an oily product. Flash chromatography (25% EtOAc/hexane) gave after crystallization from hexane **209** (3.0 g).

A solution of **209** (1.2 g) and rhodium trichloride hydrate (60 mg) in ethanol (100 mL) was refluxed for 2 h. The mixture was cooled to 60°, 1N hydrochloric acid (20 mL) was added, and the mixture was stirred at 60° for 2 h. The cooled mixture was partitioned between water and ethyl acetate, and the organic layer was washed with aqueous sodium bicarbonate and brine, dried and evaporated to a solid. Flash chromatography (50-75% ether/hexane) followed by crystallization from methylene chloride-hexane afforded the title compound (840 mg, 78%, mp 185-186°C) as colorless crystals.

Example 16

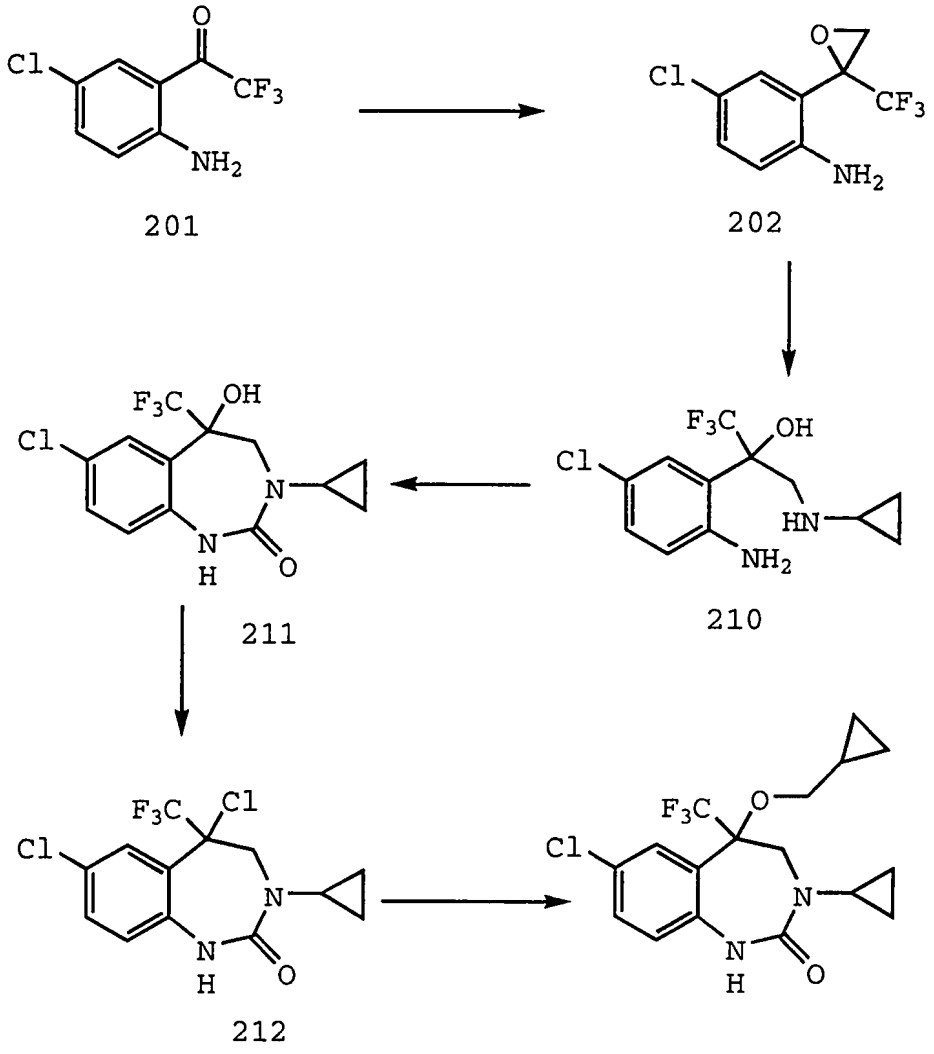
Preparation of (S)-7-chloro-5-(cyclopropylmethyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one



Racemic 7-chloro-5-(cyclopropylmethyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one (1.2 g) was separated into its constituent enantiomers on a Chiralcel-OD-AMB liquid chromatography column (10% EtOH-hexane). The faster eluting enantiomer was crystallized from ethyl acetate-hexane to give the title compound (335 mg, mp 190-191°C) which has been assigned the (S) absolute configuration.

Example 17

Preparation of 7-chloro-3-cyclopropyl-5-(cyclopropylmethoxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one



To a solid mixture of 95% sodium hydride (1.94 g, 81 mmol) and trimethylsulfoxonium iodide (17.8 g, 81 mmol) was added dropwise with stirring over 20 min, 100 mL of dry DMSO. After an additional 20 min of stirring at ambient temperature, hydrogen evolution had ceased, and a solution of **201** (10 g, 44.7 mmol) in dry THF (200 mL) was run in over 5 min. After an additional 2 min, the reaction was quenched with water. The reaction mixture was poured onto water and extracted with ether. The ether layer was washed twice with

brine and was dried over magnesium sulfate. Ethanol (35 mL) was added to this ethereal solution and this was concentrated at 20° under reduced pressure to a volume of 35 mL. Cyclopropylamine (12.4 mL, 179 mmol) was added and the solution was stirred overnight at ambient temperature and then 2 h at 50° after which time it was concentrated at 40° to **210** (9.4 g) as an oily product.

To a solution of **210** (9.4 g, 31.9 mmol) in 250 mL of dry THF was added N,N'-carbonyldiimidazole (9.3 g, 57.4 mmol) and the reaction mixture was stirred overnight at ambient temperature and evaporated to a solid. Ethanol (150 mL), and triethylamine (13 mL) was added and the mixture was refluxed for 4 h and then evaporated to a small volume. This was taken up in ethyl acetate, and this solution was washed with water, aqueous citric acid, and brine, dried over sodium sulfate and concentrated to an oil. Crystallization from ethyl acetate hexane afforded 2.6 g of a crystalline product. Flash chromatography of the mother liquor on silica gel (40-50% ethyl acetate-hexane) afforded an additional 1.7 g for a total of 4.3 g (42%) of **211** as colorless crystals.

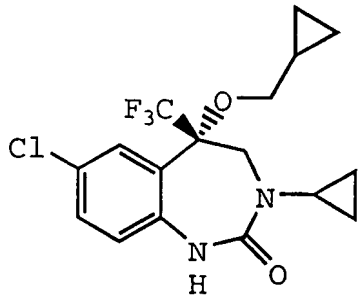
To a solution of **211** (4.3 g, 13.4 mmol) and pyridine (1.6 mL, 20.1 mmol) in 48 mL of dry THF at 0° was added dropwise thionyl chloride (2.0 mL). After addition was complete, the cooling bath was removed, and stirring was continued at ambient temperature for 20 min. The reaction mixture was partitioned between water and ethyl acetate, and the organic layer was washed with brine, dried and evaporated to **212** as a crystalline product (4.2 g).

To a solution of cyclopropylmethanol (9 mL) in 75 mL of dry DMSO was added 100% sodium hydride (840 mg). This was stirred for 1 h at ambient temperature until hydrogen evolution ceased after which time **212** (4.0 g, 11.8 mmol) in DMSO (25 mL) was added. After stirring at ambient temperature for 1 h, the reaction mixture was partitioned between ethyl ether and aqueous citric acid, and the organic

layer was washed with brine, dried (sodium sulfate) and evaporated to an oily product. Flash chromatography on silica gel (10-60% EtOAc-hexane) gave after crystallization from ethyl acetate -hexane the title compound (2.15 g, 49%, mp 153.5-155°C) as colorless crystals.

Example 18

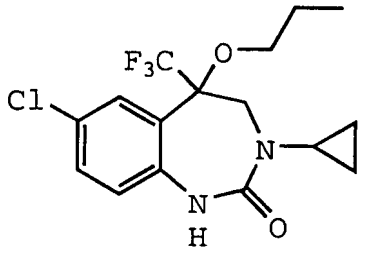
Preparation of (S)-7-chloro-3-cyclopropyl-5-(cyclopropylmethoxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one



Racemic 7-chloro-3-cyclopropyl-5-(cyclopropylmethoxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one (1.1 g) was separated into its constituent enantiomers on a Chiralcel OD-H liquid chromatography column (10% EtOH-supercritical carbon dioxide). The faster eluting enantiomer was crystallized from hexane to give the title compound (320 mg, mp 66-68°) which has been assigned the (S) absolute configuration.

Example 19

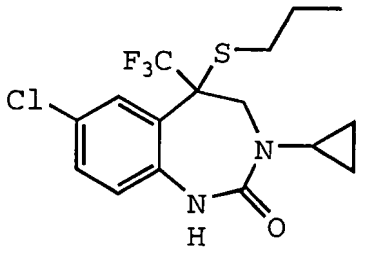
Preparation of 7-chloro-3-cyclopropyl-5-propyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one



The title compound (mp 153-154°) is prepared according to the method of Example 17 by substituting propanol for cyclopropylmethanol.

Example 20

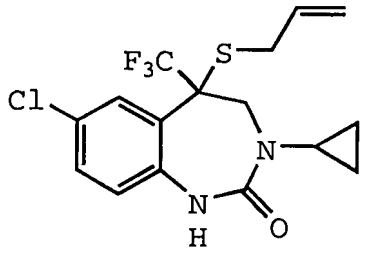
Preparation of 7-chloro-3-cyclopropyl-5-propylthio-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one



The title compound (mp 150-151°C) is prepared according to the method of Example 17 by substituting propanethiol for cyclopropylmethanol.

Example 21

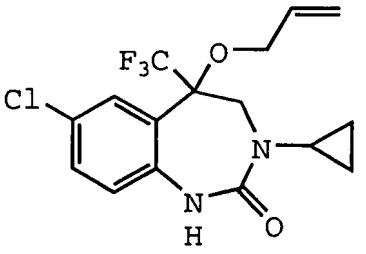
Preparation of 7-chloro-3-cyclopropyl-5-allylthio-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one



The title compound (mp 144-145.5°C) is prepared according to the method of Example 17 by substituting allyl mercaptan for cyclopropylmethanol.

Example 22

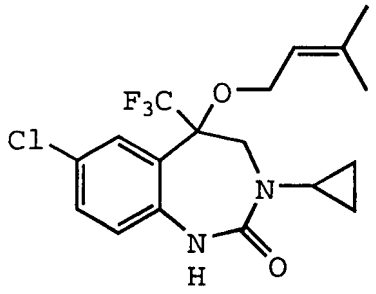
Preparation of 7-chloro-3-cyclopropyl-5-allyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one



The title compound (mp 120-121°C) is prepared according to the method of Example 17 by substituting allyl alcohol for cyclopropylmethanol.

Example 23

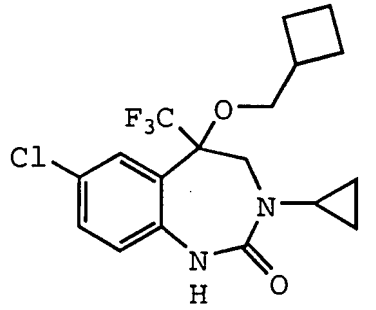
Preparation of 7-chloro-3-cyclopropyl-5-(3-methyl-2-butenyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one



The title compound (mp 130-131°C) is prepared according to the method of Example 17 by substituting 3-methyl-2-butenol for cyclopropylmethanol.

Example 24

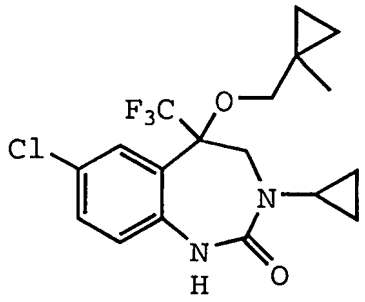
Preparation of 7-chloro-3-cyclopropyl-5-cyclobutylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one



The title compound (mp 158-159°C) is prepared according to the method of Example 17 by substituting cyclobutylmethanol for cyclopropylmethanol.

Example 25

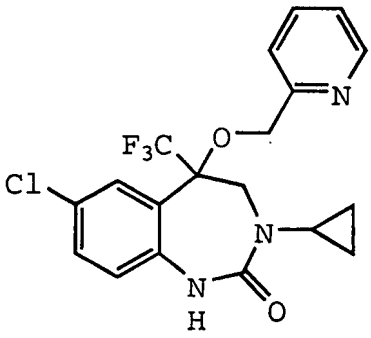
Preparation of 7-chloro-3-cyclopropyl-5-(1-methylcyclopropyl)methyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one



The title compound (mp 166-167°C) is prepared according to the method of Example 17 by substituting (1-methylcyclopropyl)methanol for cyclopropylmethanol.

Example 26

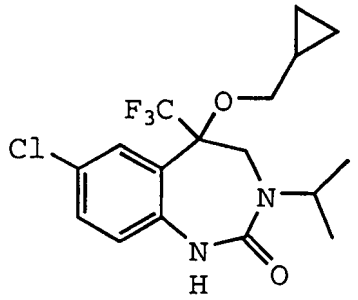
Preparation of 7-chloro-3-cyclopropyl-5-(2-pyridyl)methyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one



The title compound is (mp 170-171.5°C) prepared according to the method of Example 17 by substituting 2-(hydroxymethyl)pyridine for cyclopropylmethanol

Example 27

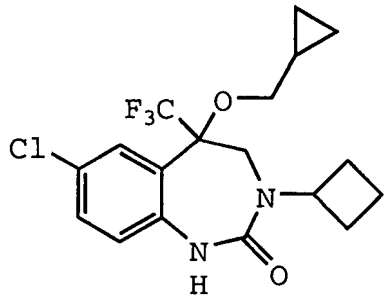
Preparation of 7-chloro-3-isopropyl-5-cyclopropylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one



The title compound (mp 169.5-170.5°C) is prepared according to the method of Example 17 by substituting isopropylamine for cyclopropylamine.

Example 28

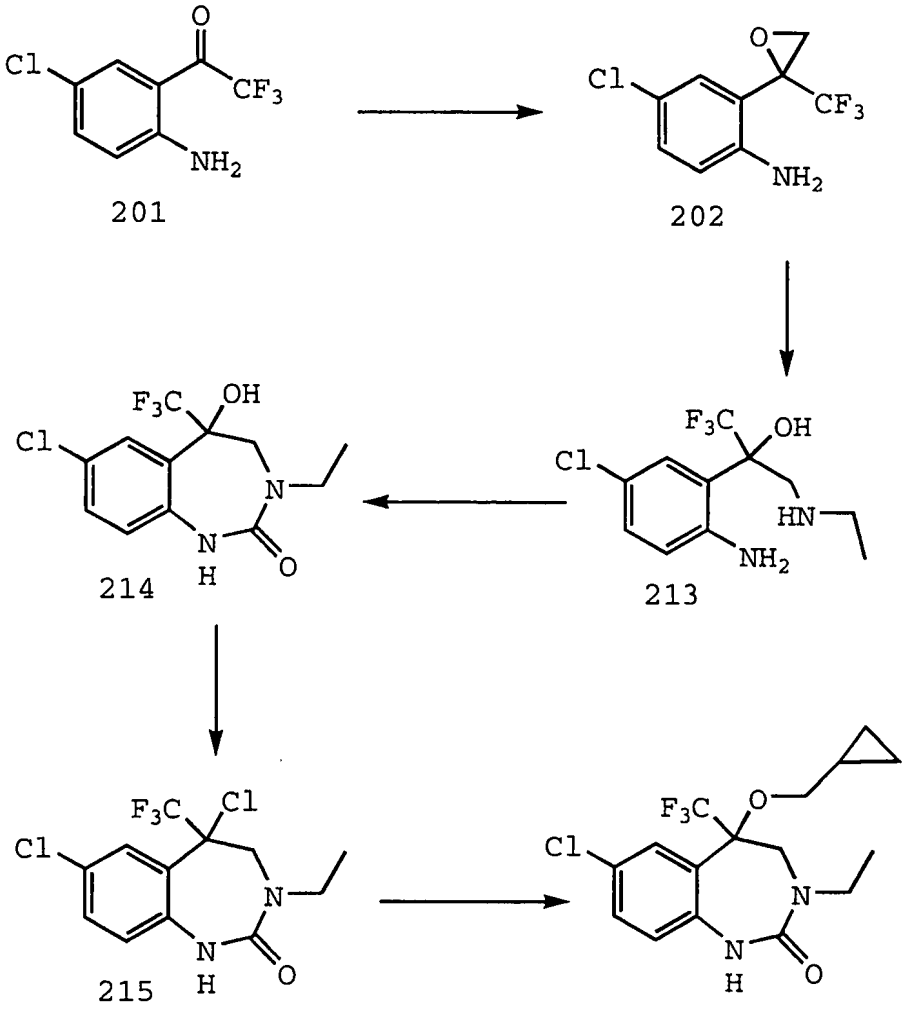
Preparation of 7-chloro-3-cyclobutyl-5-cyclopropylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one



The title compound (mp 156°C) is prepared according to the method of Example 17 by substituting cyclobutylamine for cyclopropylamine.

Example 29

Preparation of 7-chloro-5-(cyclopropylmethoxy)-1,5-dihydro-3-ethyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one



A solution of approximately 28 mmoles of diazomethane in 100 mL of ether was generated from 10 g of Diazald® following the directions provided by the vender (Aldrich Chemical Company). This solution was added to a solution of **201** (5.2 g, 23.2 mmoles) in 20 mL of ether and the reaction mixture was stirred for 3 hr at room temperature at which time tlc showed complete conversion to epoxide **202**. Excess diazomethane was quenched by the addition of acetic acid, 20 mL of ethanol was added, and the solution was concentrated to a volume of approximately 20 mL on a rotary evaporator. To this solution was added 20 mL of a solution of 2M

ethylamine in THF and the mixture was stirred in a stoppered flask at 50° for 5 h. Evaporation of the solvent under reduced pressure afforded after purification by flash chromatography on silica gel (20% ethylacetate-hexane) **213** (2.7 g) as an oil.

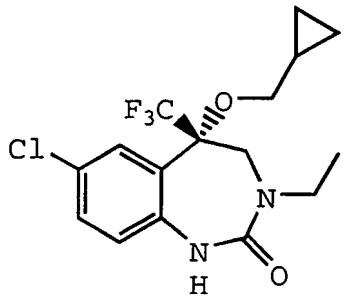
To a solution of **213** (2.7 g) in 45 mL of dry THF was added N,N'-carbonyldiimidazole (1.8 g), and triethylamine (4.2 mL) and the reaction mixture was stirred overnight at ambient temperature. Ethanol (15 mL) was added and the mixture was refluxed for 3 h, then evaporated to a small volume. This was taken up in ethyl acetate, and this solution was washed eith water, aqueous citric acid, and brine, dried over sodium sulfate and concentrated to an oil. Addition of methylene chloride precipitated the product and **214** was collected as colorless crystals (1.73 g).

To a solution of **214** (1.54 g) and pyridine (0.50 mL) in 20 mL of dry THF at 0° was added dropwise thionyl chloride (0.400 mL) After addition was complete, the cooling bath was removed, and stirring was continued at ambient temperature for 1 h. The reaction mixture was partitioned between water and ethyl acetate, and the organic layer which contained both dissolved and undissolved product was evaporated to **215** as a crystalline product (1.43 g).

To a solution of cyclopropylmethanol (0.20 mL) in 3 mL of dry DMSO was added 100% sodium hydride (36 mg). This was stirred for 30 min at ambient temperature until hydrogen evolution ceased after which time **215** (150 mg) was added in one portion. After stirring at ambient temperature for 20 min, the reaction mixture was partitioned between ethyl acetate and aqueous citric acid, and the organic layer was washed with brine, dried (sodium sulfate) and evaporated to a solid product. This was recrystallized from ethyl acetate-hexane to afford the title compound (85 mg, mp 157-159°) as colorless crystals.

Example 30

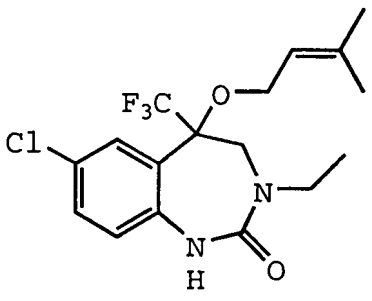
Preparation of (S)-7-chloro-5-(cyclopropylmethyloxy)-1,5-dihydro-3-ethyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one



Racemic 7-chloro-5-(cyclopropylmethyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one (1.7 g) was separated into its constituent enantiomers on a Chiralcel-OD-H liquid chromatography column (10% EtOH-supercritical carbon dioxide). The faster eluting enantiomer was the title compound (603 mg, Mass Spec. $(M+H)^+$ Calc. for $C_{16}H_{19}F_3N_2O_2Cl$: 363.17076; Fd: 363.17088) as an amorphous solid which has been assigned the (S) absolute configuration.

Example 31

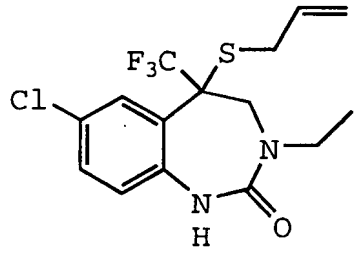
Preparation of 7-chloro-3-ethyl-5-(3-methyl-2-butenyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one



The title compound (mp 158-160°C) is prepared according to the method of Example 29 by substituting 3-methyl-2-butenol for cyclopropylmethanol.

Example 32

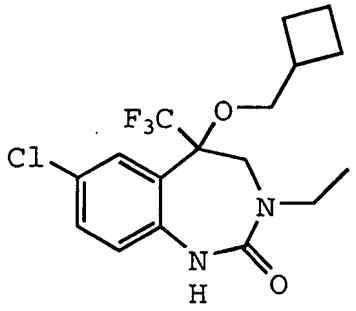
Preparation of 7-chloro-3-ethyl-5-allylthio-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one



The title compound (mp 138.1-141.8°C) is prepared according to the method of Example 29 by substituting allyl mercaptan for cyclopropylmethanol.

Example 33

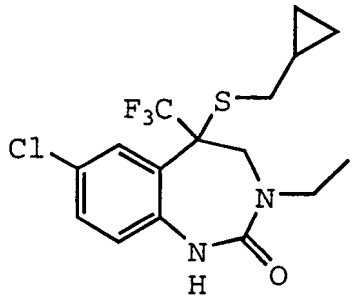
Preparation of 7-chloro-3-ethyl-5-cyclobutylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one



The title compound (Mass Spec. $(M+H)^+$ Calc. for $C_{17}H_{21}F_3N_2O_2Cl$: 377.1244; Fd: 377.1262) is prepared according to the method of Example 29 by substituting cyclobutylmethanol for cyclopropylmethanol.

Example 34

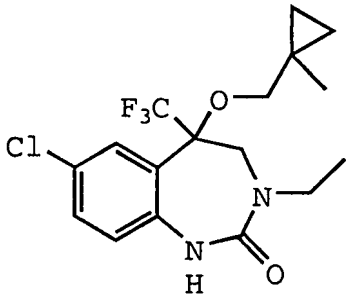
Preparation of 7-chloro-3-ethyl-5-cyclopropylmethylthio-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one



The title compound (mp 152.3-156°C) is prepared according to the method of Example 29 by substituting cyclopropylmethyl mercaptan for cyclopropylmethanol.

Example 35

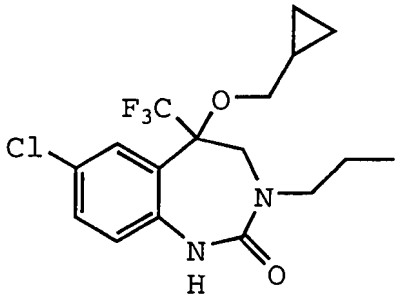
Preparation of 7-chloro-3-ethyl-5-(1-methylcyclopropyl)methyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one



The title compound (mp 171-172.5°C) is prepared according to the method of Example 29 by substituting (1-methylcyclopropyl)methanol for cyclopropylmethanol.

Example 36

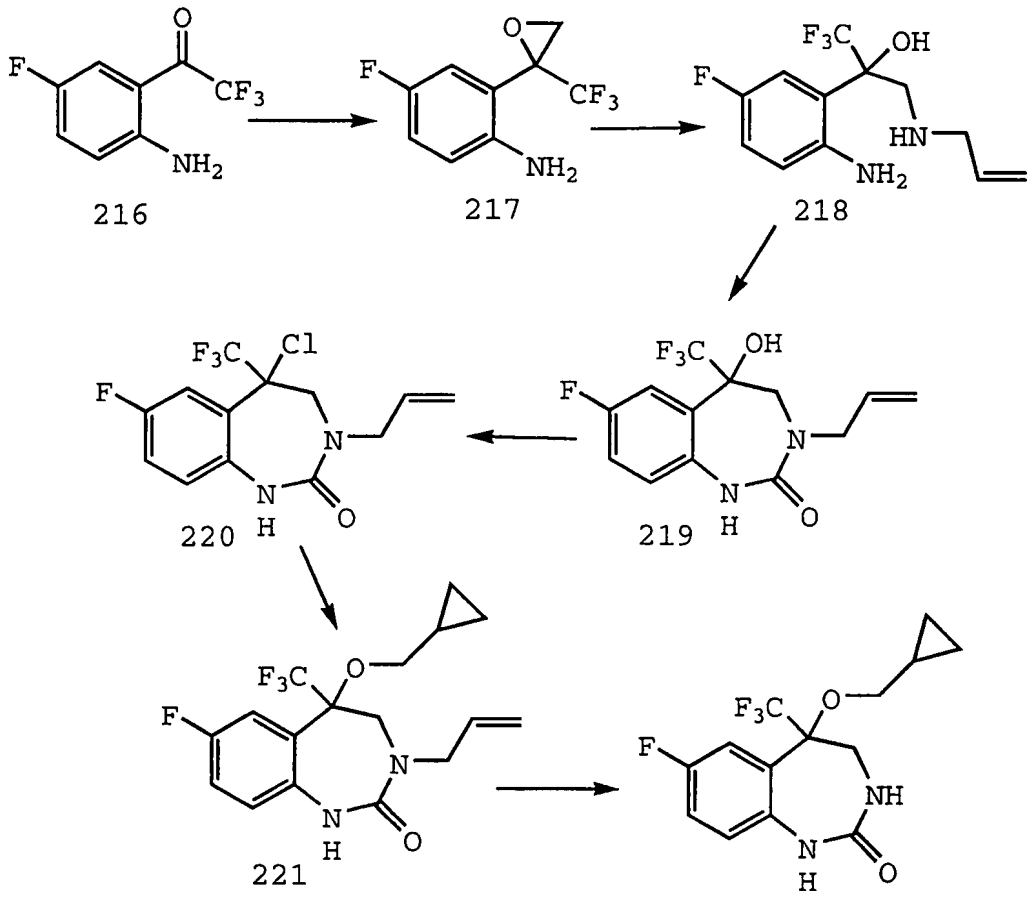
Preparation of 7-chloro-3-propyl-5-cyclopropylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one



The title compound (mp 155.5-157.5°C) is prepared according to the method of Example 29 by substituting n-propylamine for ethylamine.

Example 37

Preparation of 7-Fluoro-5-(cyclopropylmethoxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one



To a 0° solution of N-pivaloyl-4-fluoroaniline (10 g) in 150 mL of dry THF was added dropwise over 20 min 1.6M butyllithium in hexane (77 mL). After stirring at 0° for 1 h, ethyltrifluoroacetate (14.0 mL) was added and the the reaction mixture was allowed to warm to room temperature over 1.5 h. The reaction was quenched by the addition of aqueous ammonium chloride and the mixture was partitioned between water and ether. The ether layer was dried and concentrated to a brown oil (18.3 g) which was used directly in the next reaction.

This oil was dissolved in 15 mL of ethylene glycol dimethyl ether, 75 mL of concentrated aqueous hydrochloric acid was added and the mixture was refluxed for 1.5 h. The

cooled reaction mixtured was diluted with water and made basic with solid sodium carbonate. This was extracted with ether, and the extractsa were dried and evaporated to an oil which was purified by flash chromatography on silica gel (10-20% ethyl acetate-hexane) to afford after recrystalization from ethyl acetate-hexane, 2.65 g of 2-amino-5-fluoro-1',1',1'-trifluoroacetophenone **216**.

A solution of approximately 15 mmoles of diazomethane in 40 mL of ether was generated from 5 g of Diazald® following the directions provided by the vender (Aldrich Chemical Company). This solution was added to a solution of 2-amino-5-fluoro-1',1',1'-trifluoroacetophenone **216** (2.65 g, 12.8 mmoles) in 10 mL of ether and the reaction mixture was stirred for 5 hr at room temperature at which time tlc showed complete conversion to epoxide **217**. Excess diazomethane was quenched by the addition of acetic acid. To one-half of this solution (containing approximately 6.5 mmol of epoxide) 10 mL of ethanol was added, and the solution was concentrated to a volume of approximately 10 mL on a rotary evaporator. To this solution was added 1.69 mL of allylamine and the mixture was stirred at room temperature overnight. Evaporation of the solvent under reduced pressure afforded a crude product which was purified by flash chromatography on silica gel (10-50% ethyl acetate-hexane) affording 1.05 g of the product **218** as an oil.

To a solution of **218** (1.05 g, 3.77 mmol) in 20 mL of dry THF was added N,N'-carbonyldiimidazole (856 mg) and triethylamine (2.6 mL) and the reaction mixture was stirred overnight at ambient temperature. Ethanol (7 mL) was added and the mixture was refluxed for 6 h. The cooled mixture was poured onto water, and this mixture was extracted twice with ethyl acetate. The combined extracts were dried over sodium sulfate and evaporated. Flash chromatography (20-50% EtOAc/hexane) gave **219** as a white solid (858 mg, 75%).

To a solution of **219** (850 mg) and pyridine (0.339 mL) in 12 mL of dry THF at 0° was added dropwise thionyl

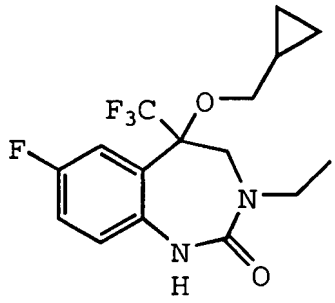
chloride (0.407 mL) After addition was complete, the cooling bath was removed, and stirring was continued at ambient temperature for 30 min. The reaction mixture was partitioned between water and ethyl acetate, and the organic layer which contained both dissolved and undissolved product was evaporated to **220** as a crystalline product (785 mg, 87%).

To a solution of cyclopropylmethanol (0.624 mL) in 5 mL of dry DMSO was added 100% sodium hydride (55 mg). This was stirred for 30 min at ambient temperature until hydrogen evolution ceased after which time **220** (250 mg) in DMSO (3.5 mL) was added in one portion. After stirring at ambient temperature for 2 h, the reaction mixture was partitioned between ether and aqueous citric acid, and the organic layer was washed with brine, dried (sodium sulfate) and evaporated to **221** (240 mg) as a solid.

A solution of **221** (135 mg) and rhodium trichloride hydrate (8 mg) in ethanol (10 mL) was refluxed for 1.5 h. The mixture was cooled to 60°, 1N hydrochloric acid (2.5 mL) was added, and the mixture was stirred at 60° for 1 h. The cooled mixture was partitioned between water and ethyl acetate, and the organic layer was washed with aqueous sodium bicarbonate and brine, dried and evaporated to an oil. Crystallization from ethyl acetate-hexane afforded the title compound (55 mg, mp 198-199°C) as a colorless solid.

Example 38

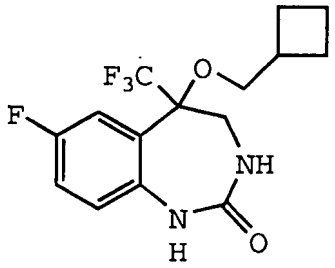
Preparation of 7-Fluoro-3-ethyl-5-cyclopropylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one



The title compound (mp 156°C) is prepared according to the method of Example 37 by substituting ethylamine for allylamine, and eliminating the final deprotection step.

Example 39

Preparation of 7-Fluoro-5-(cyclobutylmethoxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one

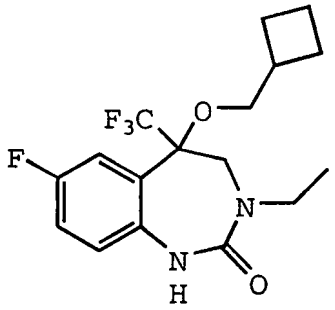


To a solution of cyclobutylmethanol (0.821 mL) in 5 mL of dry DMSO was added 100% sodium hydride (63 mg). This was stirred for 30 min at ambient temperature until hydrogen evolution ceased after which time **220** (280 mg) in DMSO (2 mL) was added in one portion. After stirring at ambient temperature for 2 h, the reaction mixture was partitioned between ether and aqueous citric acid, and the organic layer was washed with brine, dried (sodium sulfate) and evaporated to a crude product which was purified by flash chromatography on silica gel to give a solid (190 mg).

This solid and rhodium trichloride hydrate (10 mg) in ethanol (13 mL) was refluxed for 1.5 h. The mixture was cooled to 60°, 1N hydrochloric acid (3.5 mL) was added, and the mixture was stirred at 60° for 1 h. The cooled mixture was partitioned between water and ethyl acetate, and the organic layer was washed with aqueous sodium bicarbonate and brine, dried and evaporated to an oil. Crystallization from methylene chloride-hexane afforded the title compound (55 mg, mp 190-191°C) as colorless crystals.

Example 40

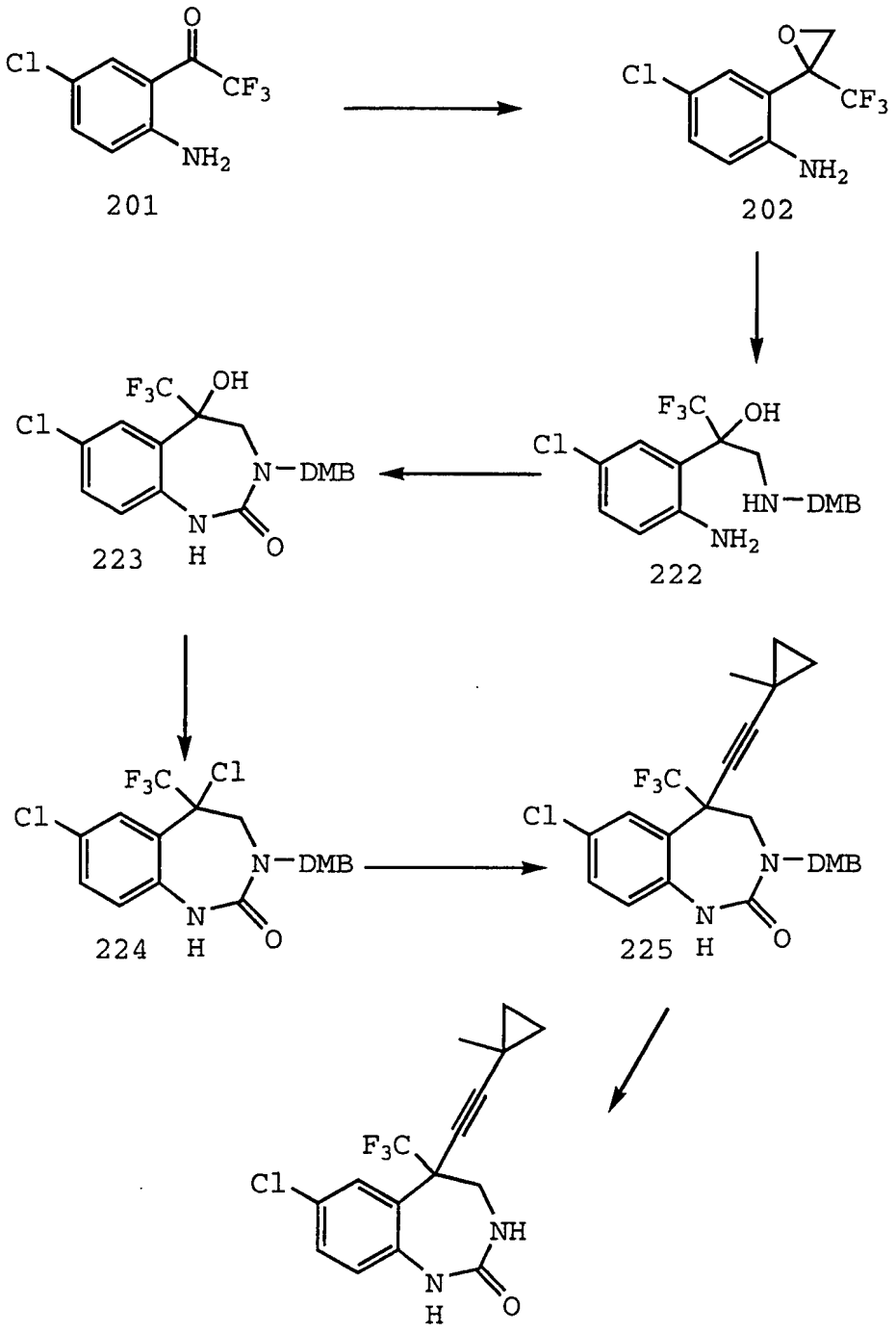
Preparation of 7-Fluoro-3-ethyl-5-cyclobutylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one



The title compound (mp 137-138°C) is prepared according to the method of Example 39 by substituting ethylamine for allylamine, and eliminating the final deprotection step.

Example 41

Preparation of 7-chloro-5-[2-(1-methylcyclopropyl)ethynyl]-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one



A solution of approximately 60 mmoles of diazomethane in 200 mL of ether was generated from 10 g of Diazald® following the directions provided by the vender (Aldrich Chemical Company). This solution was added to a solution of

201 (11.15 g, 50 mmoles) in 30 mL of ether and the reaction mixture was stirred for 5 hr at room temperature at which time tlc showed complete conversion to epoxide **202**. Excess diazomethane was quenched by the addition of acetic acid, 2,4-dimethoxybenzylamine (12 g), and 50 mL of ethanol was added, and the solution was concentrated to a volume of approximately 60 mL on a rotary evaporator. The mixture was stirred overnight at ambient temperature and then for 4 h at 50°. After evaporation of the solvent under reduced pressure, the crude product was dissolved in ether and this solution was washed twice with water. The ether layer was extracted twice with 1N HCl, and the combined extracts were made basic with 1N NaOH and then extracted with ether. The ether extracts were dried and evaporated and the crude product was redissolved in methylene chloride and this solution was washed with 1% aqeous acetic acid, and brine, dried and evaporated to **222** (13.2 g, 65%).

To a solution of **222** (13.0 g) in 150 mL of dry THF was added N,N'-carbonyldiimidazole (6.5 g), and triethylamine (13 mL) and the reaction mixture was stirred 4 h at ambient temperature. Ethanol (75 mL) was added and the mixture was refluxed overnight, then evaporated to a small volume. This was diluted with water and extracted twice with ethyl acetate. The combined extracts were dried and evaporated to a solid which upon trituration with methylene chloride afforded **223** as colorless crystals (10.1 g, 73%).

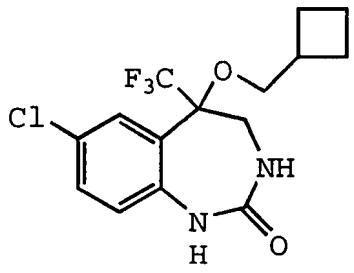
To a solution of **223** (2.92 g, 6.75 mmol) and pyridine (0.685 mL, 1.2 equiv) in 30 mL of dry THF at 0° was added dropwise thionyl chloride (0.540 mL, 1.1 equiv). After addition was complete, the cooling bath was removed, and stirring was continued at ambient temperature for 1 h. The reaction mixture was partitioned between water and ethyl acetate, and the organic layer which contained both dissolved and undissolved product was evaporated to **224** as a crystalline product (2.4 g, 79%).

To a solution of (1-methylcyclopropyl)acetylene (144 mg, 1.8 mmol) in dry THF (4 mL) at 0° was added 1.6 M butyllithium in hexane (0.99 mL, 1.58 mmol). After 30 min at 0°, the mixture was cooled to -30° and **224** (200 mg, 0.45 mmol) in THF (2 mL) was added dropwise. The reaction mixture was allowed to warm to 0° over 30 min after which time it was poured onto aqueous citric acid and extracted twice with ether. The combined extracts were washed with brine, dried and evaporated to 260 mg of **225** as a solid which was used directly in the next reaction.

A solution of **225** (250 mg) in trifluoroacetic acid (1.5 mL) was stirred at room temperature for 30 min then poured onto aqueous sodium bicarbonate and extracted with ethyl acetate. The combined extracts were washed with brine, dried and evaporated to an impure solid which was purified by flash chromatography on silica gel (20-80% ethyl acetate-hexane) followed by recrystallization from ether-ethyl acetate-hexane to afford the title compound (6 mg, mp 196-198°) as colorless crystals.

Example 42

Preparation of 7-chloro-5-cyclobutylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one



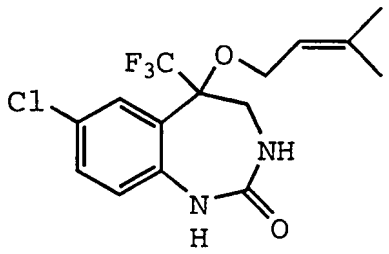
To a solution of cyclobutylmethanol (0.456 mL) in 7 mL of dry THF at room temperature was added sodium hydride (110 mg). After 30 min, chloride **224** (300 mg) in THF (3.5 mL) was added and the reaction mixture was stirred at ambient temperature for 1 h. The reaction was poured onto saturated

ammonium chloride and was extracted with ethyl acetate. The extracts dried over magnesium sulfate and evaporated to give a crude product which was purified by flash chromatography (20-40% EtOAc/hexane) gave 124 mg solid product.

A solution of this material in 2.5 mL of trifluoroacetic acid was stirred at room temperature for 30 min and then partitioned between ethyl acetate and aqueous sodium bicarbonate. The organic phase was dried and evaporated to a crude product which was purified by flash chromatography on silica gel (50% ethyl acetate-hexane) to afford the title compound (74 mg, mp 201.6-202.9°C) as colorless crystals.

Example 43

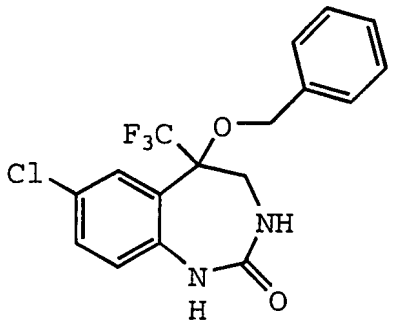
Preparation of 7-chloro-5-(3-methyl-2-butenyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one



The title compound (^{19}F NMR: δ -75.638 ppm) is prepared according to the method of Example 42 by substituting 3-methyl-2-buten-1-ol for cyclobutylmethanol.

Example 44

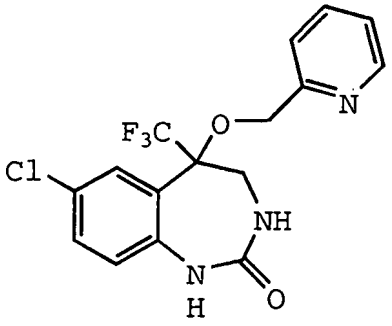
Preparation of 7-chloro-5-(phenylmethyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one



The title compound (mp 177-178°C) is prepared according to the method of Example 42 by substituting benzyl alcohol for cyclobutylmethanol.

Example 45

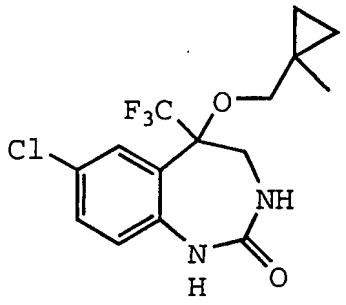
Preparation of 7-chloro-5-[(2-pyridyl)methyloxy]-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one



The title compound (mp 233-235°C) is prepared according to the method of Example 42 by substituting pyridine-2-methanol for cyclobutylmethanol.

Example 46

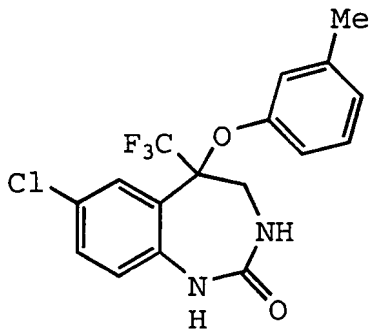
Preparation of 7-chloro-5-[(1-methylcyclopropyl)methyoxy]-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one



The title compound (mp 211-212°C) is prepared according to the method of Example 42 by substituting (1-methylcyclopropy)methanol for cyclobutylmethanol.

Example 47

Preparation of 7-chloro-5-(3-methylphenyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one

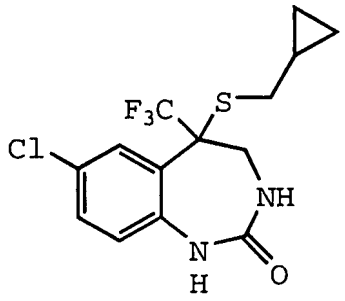


To a solution of m-cresol (0.259 mL) in 5 mL of dry THF at room temperature was added sodium hydride (41 mg). After 10 min, chloride **224** (300 mg) in THF (3.5 mL) was added and the reaction mixture was stirred at ambient temperature for 1 h. The reaction was poured onto saturated ammonium chloride and was extracted with ethyl acetate. The extracts dried over magnesium sulfate and evaporated to give a white solid.

A solution of this material in 3 mL of trifluoroacetic acid was stirred at room temperature for 2 h and then partitioned between ethyl acetate and aqueous sodium bicarbonate. The organic phase was dried and evaporated to a crude product which was purified by flash chromatography on silica gel (35-50% ethyl acetate-hexane). Crystallization from chloroform and recrystallization from 10% ethyl acetate hexane afforded the title compound (25 mg,mp 137.1-140°C) as colorless crystals.

Example 48

Preparation of 7-chloro-5-(cyclopropylmethylthio)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one

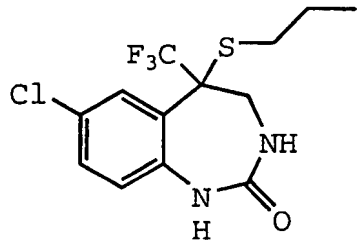


To a solution of cyclopropylmethyl mercaptan (532 mg) in 2.3 mL of dry THF at room temperature was added sodium hydride (41 mg). After 10 min,chloride **224** (200 mg) was added and the reaction mixture was stirred at ambient temperature for 1.5 h. The reaction was poured onto saturated ammonium chloride and was extracted with ethyl acetate. The extracts dried over magnesium sulfate and evaporated to give a white solid.

A solution of this material in 3 mL of trifluoroacetic acid was stirred at room temperature for 2 h and then partitioned between ethyl acetate and aqueous sodium bicarbonate. The organic phase was dried and evaporated to a solid product which was twice from methylene chloride-hexane to afford the title compound (mp 175-177°C) as a colorless solid.

Example 49

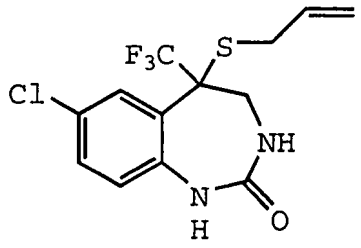
Preparation of 7-chloro-5-(propylthio)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one



The title compound (mp 156-157°C) is prepared according to the method of Example 48 by substituting propanethiol for cyclopropylmethyl mercaptan.

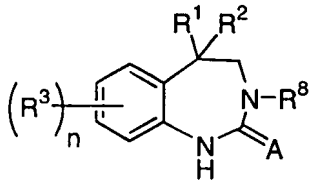
Example 50

Preparation of 7-chloro-5-(2-propenylthio)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one



The title compound (mp 147.3-149°C) is prepared according to the method of Example 48 by substituting allyl mercaptan for cyclopropylmethyl mercaptan.

Table 1*



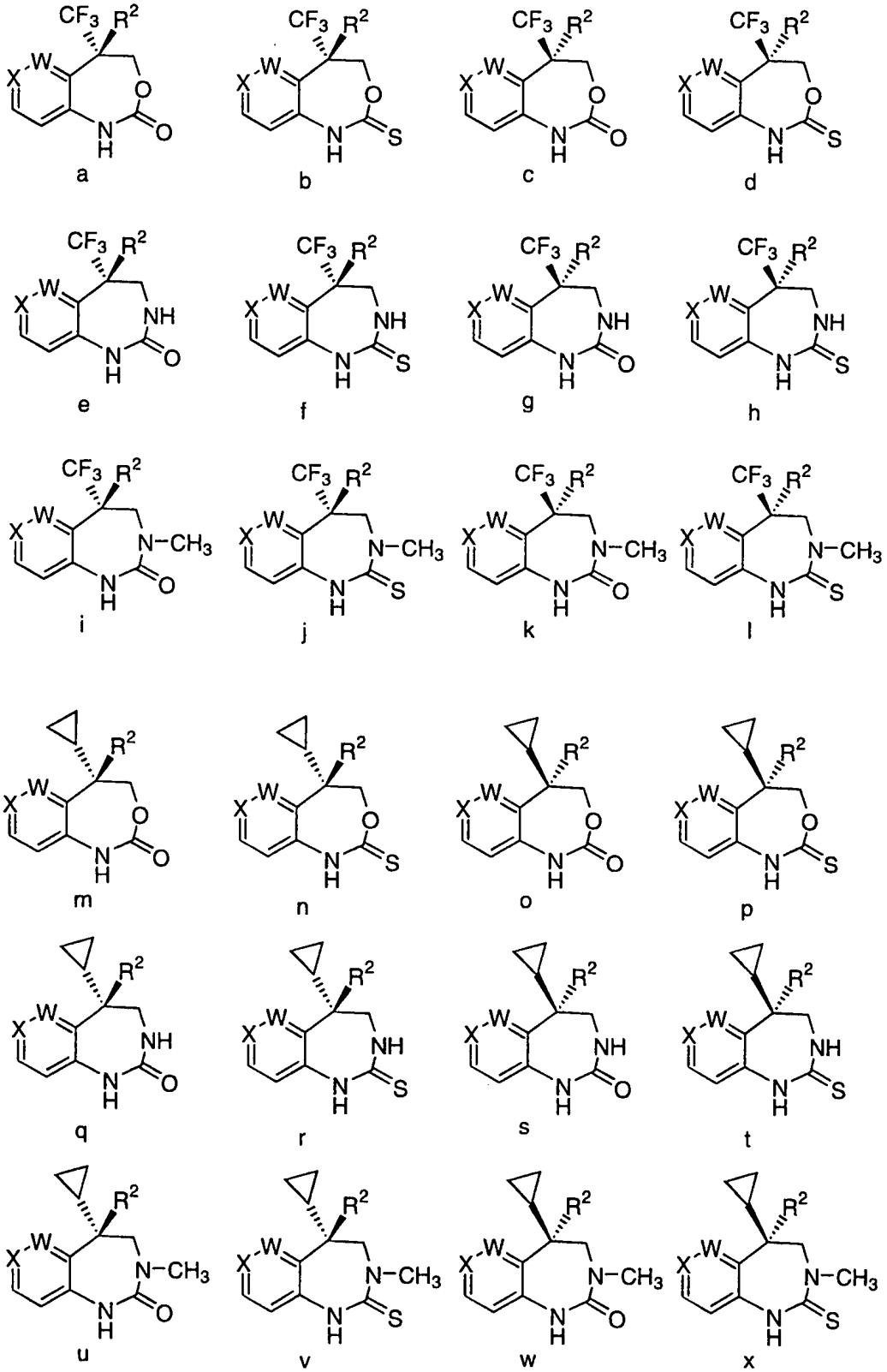
Ex.#	R^3	R^1	R^2	A	R^8	m.p. (°C)
1	7-Cl	CF_3	C≡C-cycPr	O	H	240-242
2	6,7-diF	CF_3	C≡C-cycPr	O	H	232-233
3	7-Cl	CF_3	C≡C-cycPr	O	H	221-223
4	7-Cl	CF_3	C≡C-cycPr	S	H	230 dec.
5	7-Cl	CF_3	n-Bu	O	H	174-176
6	7-Cl	CF_3	C≡C-cycPr	O	CH_3	177-178
7	7-Cl	CF_3	C≡C-cycPr	O	Et	186-188
8	7-Cl	CF_3	C≡C-cycPr	O	CyPr	195-196
9	7-Cl	CF_3	C≡C-cycPr	O	Et	192-193
10	7-Cl	CF_3	C≡C-cycPr	O	CyPr	181-182
11	7-Cl	CF_3	OCH_2-cycPr	O	CH_3	163-165
12	7-Cl	CF_3	OCH_2-C=C(Cl)$_2$	O	CH_3	148.6-149.9
13	7-Cl	CF_3	OCH_2-C≡CH_3	O	CH_3	229.7-232.1
14	7-Cl	CF_3	OCH_2-(2-F-6-CH_3O-phenyl)	O	CH_3	172.1-173.8
15	7-Cl	CF_3	OCH_2-cycPr	O	H	185-186
16(S)	7-Cl	CF_3	OCH_2-cycPr	O	H	190-191
17	7-Cl	CF_3	OCH_2-cycPr	O	CyPr	153.5-155
18(S)	7-Cl	CF_3	OCH_2-cycPr	O	CyPr	66-68

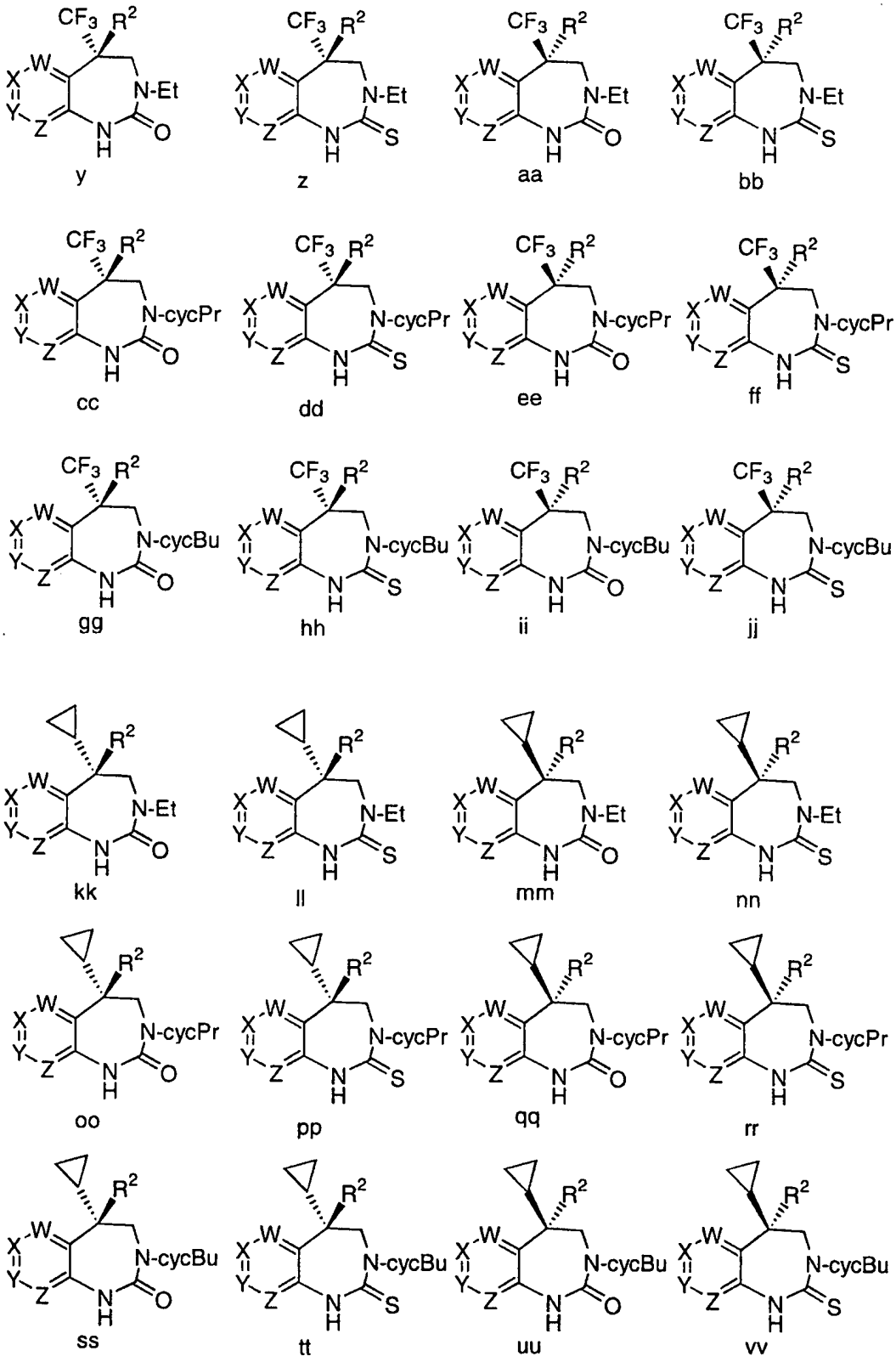
19	7-Cl	CF_3	$OCH_2CH_2CH_3$	O	CyPr	153-154
20	7-Cl	CF_3	$SCH_2CH_2CH_3$	O	CyPr	150-151
21	7-Cl	CF_3	$SCH_2C{=}CH_2$	O	CyPr	144-145.5
22	7-Cl	CF_3	$OCH_2C{=}CH_2$	O	CyPr	120-121
23	7-Cl	CF_3	$OCH_2C{=}C(CH_3)_2$	O	CyPr	130-131
24	7-Cl	CF_3	OCH_2cycBu	O	CyPr	158-159
25	7-Cl	CF_3	OCH_2-(1-CH_3-cycPr)	O	CyPr	166-167
26	7-Cl	CF_3	OCH_2-pyrid-2-yl	O	CyPr	170-171.5
27	7-Cl	CF_3	OCH_2-cycPr	O	i-Pr	169.5-170.5
28	7-Cl	CF_3	OCH_2-cycPr	O	CyBu	156
29	7-Cl	CF_3	OCH_2-cycPr	O	Et	157-159
30(s)	7-Cl	CF_3	OCH_2-cycPr	O	Et	
31	7-Cl	CF_3	$OCH_2C{=}C(CH_3)_2$	O	Et	158-160
32	7-Cl	CF_3	$SCH_2C{=}CH_2$	O	Et	138.1-141.8
33	7-Cl	CF_3	OCH_2-cycBu	O	Et	
34	7-Cl	CF_3	SCH_2-cycPr	O	Et	152.3-156
35	7-Cl	CF_3	OCH_2-(1-CH_3-cycPr)	O	Et	171-172.5
36	7-Cl	CF_3	OCH_2-cycPr	O	n-Pr	155.5-157.5
37	7-F	CF_3	OCH_2-cycPr	O	H	198-199
38	7-F	CF_3	OCH_2-cycPr	O	Et	156
39	7-F	CF_3	OCH_2-cycBu	O	H	190-191
40	7-F	CF_3	OCH_2-cycBu	O	Et	137-138
41	7-Cl	CF_3	$C{\equiv}C$-(1-CH_3-cycPr)	O	H	196-198

42	7-Cl	CF_3	OCH_2cycBu	O	H	201.6-202.9
43	7-Cl	CF_3	$OCH_2C=C(CH_3)_2$	O	H	
44	7-Cl	CF_3	OCH_2-phenyl	O	H	177-178
45	7-Cl	CF_3	OCH_2-pyrid-2-yl	O	H	233-235
46	7-Cl	CF_3	OCH_2-(1-CH_3-cycPr)	O	H	211-212
47	7-Cl	CF_3	O-(3-CH_3-phenyl)	O	H	137.1-140
48	7-Cl	CF_3	SCH_2-cycPr	O	H	175-177
49	7-Cl	CF_3	$SCH_2CH_2CH_3$	O	H	156-157
50	7-Cl	CF_3	$SCH_2C=CH_2$	O	H	147.3-149

*Unless otherwise indicated, stereochemisty is (+/-).

Table 2*





Ex.#	W	X	R^2
1.	CH	CH	C≡C-cycPr
2.	CH	CH	C≡C-(1-CH_3-cycPr)

3.	CH	CH	C≡C-iPr
4.	CH	CH	C≡C-nPr
5.	CH	CH	C≡C-Bu
6.	CH	CH	C≡C-iBu
7.	CH	CH	C≡C-tBu
8.	CH	CH	C≡C-Et
9.	CH	CH	C≡C-Me
10.	CH	CH	C≡C-Ph
11.	CH	CH	C≡C-2-Pyridyl
12.	CH	CH	C≡C-3-Pyridyl
13.	CH	CH	C≡C-4-Pyridyl
14.	CH	CH	C≡C-2-furanyl
15.	CH	CH	C≡C-3-furanyl
16.	CH	CH	C≡C-2-thienyl
17.	CH	CH	C≡C-3-thienyl
18.	CH	CH	CH=CH-cycPr
19.	CH	CH	CH=CH-iPr
20.	CH	CH	CH=CH-nPr
21.	CH	CH	CH=CH-Bu
22.	CH	CH	CH=CH-iBu
23.	CH	CH	CH=CH-tBu
24.	CH	CH	CH=CH-Et
25.	CH	CH	CH=CH-Me
26.	CH	CH	CH=CH-Ph
27.	CH	CH	CH=CH-2-Pyridyl
28.	CH	CH	CH=CH-3-Pyridyl
29.	CH	CH	CH=CH-4-Pyridyl
30.	CH	CH	CH=CH-2-furanyl
31.	CH	CH	CH=CH-3-furanyl
32.	CH	CH	CH=CH-2-thienyl
33.	CH	CH	CH=CH-3-thienyl
34.	CH	CH	$CH_2CH_2CH_2CH_2CH_3$
35.	CH	CH	$CH_2CH_2CH(CH_3)_2$
36.	CH	CH	$CH_2CH_2CH_2CH_3$
37.	CH	CH	$CH_2CH_2CH_3$
38.	CH	CH	CH_2CH_2-cycPr
39.	CH	CH	CH_2CH_2-(1-CH_3-cycPr)
40.	CH	CH	CH_2CH_2-tBu
41.	CH	CH	CH_2CH_2-cycBu

42.	CH	CH	CH_2CH_2-(1-CH_3-cycBu)
43.	CH	CH	CH_2CH_2-2-Pyridyl
44.	CH	CH	CH_2CH_2-3-Pyridyl
45.	CH	CH	CH_2CH_2-4-Pyridyl
46.	CH	CH	CH_2CH_2-2-furanyl
47.	CH	CH	CH_2CH_2-3-furanyl
48.	CH	CH	CH_2CH_2-2-thienyl
49.	CH	CH	CH_2CH_2-3-thienyl
50.	CH	CH	$CH_2C{\equiv}C$-cycPr
51.	CH	CH	$CH_2C{\equiv}C$-2-furanyl
52.	CH	CH	$CH_2CH{=}CH$-cycPr
53.	CH	CH	$CH_2CH{=}CH$-2-furanyl
54.	CH	CH	$CH{=}CHCH_2$-cycPr
55.	CH	CH	$CH{=}CHCH_2$-2-furanyl
56.	CH	CH	$OCH_2C{=}C(CH_3)_2$
57.	CH	CH	*E*-$OCH_2C{=}CHCH_3$
58.	CH	CH	*Z*-$OCH_2C{=}CHCH_3$
59.	CH	CH	OCH_2CH_3
60.	CH	CH	$OCH_2CH_2CH_3$
61.	CH	CH	$OCH_2C{=}C(Cl)_2$
62.	CH	CH	$OCH_2C{=}CH_2$
63.	CH	CH	$OCH_2C{\equiv}CCH_3$
64.	CH	CH	$OCH_2CH_2CH_3$
65.	CH	CH	OCH_2-cycPr
66.	CH	CH	OCH_2-(1-CH_3-cycPr)
67.	CH	CH	OCH_2-cycBu
68.	CH	CH	OCH_2-(1-CH_3-cycBu)
69.	CH	CH	OCH_2-Phenyl
70.	CH	CH	OCH_2CH_2-cycPr
71.	CH	CH	$OCH_2CH{=}$cycPr
72.	CCl	CH	$C{\equiv}C$-cycPr
73.	CCl	CH	$C{\equiv}C$-(1-CH_3-cycPr)
74.	CCl	CH	$C{\equiv}C$-iPr
75.	CCl	CH	$C{\equiv}C$-nPr
76.	CCl	CH	$C{\equiv}C$-Bu
77.	CCl	CH	$C{\equiv}C$-iBu

78.	CCl	CH	C≡C-tBu
79.	CCl	CH	C≡C-Et
80.	CCl	CH	C≡C-Me
81.	CCl	CH	C≡C-Ph
82.	CCl	CH	C≡C-2-Pyridyl
83.	CCl	CH	C≡C-3-Pyridyl
84.	CCl	CH	C≡C-4-Pyridyl
85.	CCl	CH	C≡C-2-furanyl
86.	CCl	CH	C≡C-3-furanyl
87.	CCl	CH	C≡C-2-thienyl
88.	CCl	CH	C≡C-3-thienyl
89.	CCl	CH	CH=CH-cycPr
90.	CCl	CH	CH=CH-iPr
91.	CCl	CH	CH=CH-nPr
92.	CCl	CH	CH=CH-Bu
93.	CCl	CH	CH=CH-iBu
94.	CCl	CH	CH=CH-tBu
95.	CCl	CH	CH=CH-Et
96.	CCl	CH	CH=CH-Me
97.	CCl	CH	CH=CH-Ph
98.	CCl	CH	CH=CH-2-Pyridyl
99.	CCl	CH	CH=CH-3-Pyridyl
100.	CCl	CH	CH=CH-4-Pyridyl
101.	CCl	CH	CH=CH-2-furanyl
102.	CCl	CH	CH=CH-3-furanyl
103.	CCl	CH	CH=CH-2-thienyl
104.	CCl	CH	CH=CH-3-thienyl
105.	CCl	CH	$CH_2CH_2CH_2CH_2CH_3$
106.	CCl	CH	$CH_2CH_2CH(CH_3)_2$
107.	CCl	CH	$CH_2CH_2CH_2CH_3$
108.	CCl	CH	$CH_2CH_2CH_3$
109.	CCl	CH	CH_2CH_2-cycPr
110.	CCl	CH	CH_2CH_2-(1-CH_3-cycPr)
111.	CCl	CH	CH_2CH_2-tBu
112.	CCl	CH	CH_2CH_2-cycBu
113.	CCl	CH	CH_2CH_2-(1-CH_3-cycBu)
114.	CCl	CH	CH_2CH_2-2-Pyridyl
115.	CCl	CH	CH_2CH_2-3-Pyridyl
116.	CCl	CH	CH_2CH_2-4-Pyridyl

117.	CCl	CH	CH_2CH_2-2-furanyl
118.	CCl	CH	CH_2CH_2-3-furanyl
119.	CCl	CH	CH_2CH_2-2-thienyl
120.	CCl	CH	CH_2CH_2-3-thienyl
121.	CCl	CH	$CH_2C{\equiv}C$-cycPr
122.	CCl	CH	$CH_2C{\equiv}C$-2-furanyl
123.	CCl	CH	$CH_2CH{=}CH$-cycPr
124.	CCl	CH	$CH_2CH{=}CH$-2-furanyl
125.	CCl	CH	$CH{=}CHCH_2$-cycPr
126.	CCl	CH	$CH{=}CHCH_2$-2-furanyl
127.	CCl	CH	$OCH_2C{=}C(CH_3)_2$
128.	CCl	CH	*E*-$OCH_2C{=}CHCH_3$
129.	CCl	CH	*Z*-$OCH_2C{=}CHCH_3$
130.	CCl	CH	OCH_2CH_3
131.	CCl	CH	$OCH_2CH_2CH_3$
132.	CCl	CH	$OCH_2C{=}C(Cl)_2$
133.	CCl	CH	$OCH_2C{=}CH_2$
134.	CCl	CH	$OCH_2C{\equiv}CCH_3$
135.	CCl	CH	$OCH_2CH_2CH_3$
136.	CCl	CH	OCH_2-cycPr
137.	CCl	CH	OCH_2-(1-CH_3-cycPr)
138.	CCl	CH	OCH_2-cycBu
139.	CCl	CH	OCH_2-(1-CH_3-cycBu)
140.	CCl	CH	OCH_2-Phenyl
141.	CCl	CH	OCH_2CH_2-cycPr
142.	CCl	CH	$OCH_2CH{=}$cycPr
143.	CH	CCl	$C{\equiv}C$-cycPr
144.	CH	CCl	$C{\equiv}C$-(1-CH_3-cycPr)
145.	CH	CCl	$C{\equiv}C$-iPr
146.	CH	CCl	$C{\equiv}C$-nPr
147.	CH	CCl	$C{\equiv}C$-Bu
148.	CH	CCl	$C{\equiv}C$-iBu
149.	CH	CCl	$C{\equiv}C$-tBu
150.	CH	CCl	$C{\equiv}C$-Et
151.	CH	CCl	$C{\equiv}C$-Me
152.	CH	CCl	$C{\equiv}C$-Ph

153.	CH	CCl	C≡C-2-Pyridyl
154.	CH	CCl	C≡C-3-Pyridyl
155.	CH	CCl	C≡C-4-Pyridyl
156.	CH	CCl	C≡C-2-furanyl
157.	CH	CCl	C≡C-3-furanyl
158.	CH	CCl	C≡C-2-thienyl
159.	CH	CCl	C≡C-3-thienyl
160.	CH	CCl	CH=CH-cycPr
161.	CH	CCl	CH=CH-iPr
162.	CH	CCl	CH=CH-nPr
163.	CH	CCl	CH=CH-Bu
164.	CH	CCl	CH=CH-iBu
165.	CH	CCl	CH=CH-tBu
166.	CH	CCl	CH=CH-Et
167.	CH	CCl	CH=CH-Me
168.	CH	CCl	CH=CH-Ph
169.	CH	CCl	CH=CH-2-Pyridyl
170.	CH	CCl	CH=CH-3-Pyridyl
171.	CH	CCl	CH=CH-4-Pyridyl
172.	CH	CCl	CH=CH-2-furanyl
173.	CH	CCl	CH=CH-3-furanyl
174.	CH	CCl	CH=CH-2-thienyl
175.	CH	CCl	CH=CH-3-thienyl
176.	CH	CCl	$CH_2CH_2CH_2CH_2CH_3$
177.	CH	CCl	$CH_2CH_2CH(CH_3)_2$
178.	CH	CCl	$CH_2CH_2CH_2CH_3$
179.	CH	CCl	$CH_2CH_2CH_3$
180.	CH	CCl	CH_2CH_2-cycPr
181.	CH	CCl	CH_2CH_2-(1-CH_3-cycPr)
182.	CH	CCl	CH_2CH_2-tBu
183.	CH	CCl	CH_2CH_2-cycBu
184.	CH	CCl	CH_2CH_2-(1-CH_3-cycBu)
185.	CH	CCl	CH_2CH_2-2-Pyridyl
186.	CH	CCl	CH_2CH_2-3-Pyridyl
187.	CH	CCl	CH_2CH_2-4-Pyridyl
188.	CH	CCl	CH_2CH_2-2-furanyl
189.	CH	CCl	CH_2CH_2-3-furanyl
190.	CH	CCl	CH_2CH_2-2-thienyl
191.	CH	CCl	CH_2CH_2-3-thienyl

192.	CH	CCl	$CH_2C\equiv C$-cycPr
193.	CH	CCl	$CH_2C\equiv C$-2-furanyl
194.	CH	CCl	$CH_2CH=CH$-cycPr
195.	CH	CCl	$CH_2CH=CH$-2-furanyl
196.	CH	CCl	$CH=CHCH_2$-cycPr
197.	CH	CCl	$CH=CHCH_2$-2-furanyl
198.	CH	CCl	$OCH_2C=C(CH_3)_2$
199.	CH	CCl	*E*-$OCH_2C=CHCH_3$
200.	CH	CCl	*Z*-$OCH_2C=CHCH_3$
201.	CH	CCl	OCH_2CH_3
202.	CH	CCl	$OCH_2CH_2CH_3$
203.	CH	CCl	$OCH_2C=C(Cl)_2$
204.	CH	CCl	$OCH_2C=CH_2$
205.	CH	CCl	$OCH_2C\equiv CCH_3$
206.	CH	CCl	$OCH_2CH_2CH_3$
207.	CH	CCl	OCH_2-cycPr
208.	CH	CCl	OCH_2-(1-CH_3-cycPr)
209.	CH	CCl	OCH_2-cycBu
210.	CH	CCl	OCH_2-(1-CH_3-cycBu)
211.	CH	CCl	OCH_2-Phenyl
212.	CH	CCl	OCH_2CH_2-cycPr
213.	CH	CCl	OCH_2CH=cycPr
214.	CCl	CCl	C≡C-cycPr
215.	CCl	CCl	C≡C-(1-CH_3-cycPr)
216.	CCl	CCl	C≡C-iPr
217.	CCl	CCl	C≡C-nPr
218.	CCl	CCl	C≡C-Bu
219.	CCl	CCl	C≡C-iBu
220.	CCl	CCl	C≡C-tBu
221.	CCl	CCl	C≡C-Et
222.	CCl	CCl	C≡C-Me
223.	CCl	CCl	C≡C-Ph
224.	CCl	CCl	C≡C-2-Pyridyl
225.	CCl	CCl	C≡C-3-Pyridyl
226.	CCl	CCl	C≡C-4-Pyridyl
227.	CCl	CCl	C≡C-2-furanyl

228.	CCl	CCl	C≡C-3-furanyl
229.	CCl	CCl	C≡C-2-thienyl
230.	CCl	CCl	C≡C-3-thienyl
231.	CCl	CCl	CH=CH-cycPr
232.	CCl	CCl	CH=CH-iPr
233.	CCl	CCl	CH=CH-nPr
234.	CCl	CCl	CH=CH-Bu
235.	CCl	CCl	CH=CH-iBu
236.	CCl	CCl	CH=CH-tBu
237.	CCl	CCl	CH=CH-Et
238.	CCl	CCl	CH=CH-Me
239.	CCl	CCl	CH=CH-Ph
240.	CCl	CCl	CH=CH-2-Pyridyl
241.	CCl	CCl	CH=CH-3-Pyridyl
242.	CCl	CCl	CH=CH-4-Pyridyl
243.	CCl	CCl	CH=CH-2-furanyl
244.	CCl	CCl	CH=CH-3-furanyl
245.	CCl	CCl	CH=CH-2-thienyl
246.	CCl	CCl	CH=CH-3-thienyl
247.	CCl	CCl	$CH_2CH_2CH_2CH_2CH_3$
248.	CCl	CCl	$CH_2CH_2CH(CH_3)_2$
249.	CCl	CCl	$CH_2CH_2CH_2CH_3$
250.	CCl	CCl	$CH_2CH_2CH_3$
251.	CCl	CCl	CH_2CH_2-cycPr
252.	CCl	CCl	CH_2CH_2-(1-CH_3-cycPr)
253.	CCl	CCl	CH_2CH_2-tBu
254.	CCl	CCl	CH_2CH_2-cycBu
255.	CCl	CCl	CH_2CH_2-(1-CH_3-cycBu)
256.	CCl	CCl	CH_2CH_2-2-Pyridyl
257.	CCl	CCl	CH_2CH_2-3-Pyridyl
258.	CCl	CCl	CH_2CH_2-4-Pyridyl
259.	CCl	CCl	CH_2CH_2-2-furanyl
260.	CCl	CCl	CH_2CH_2-3-furanyl
261.	CCl	CCl	CH_2CH_2-2-thienyl
262.	CCl	CCl	CH_2CH_2-3-thienyl
263.	CCl	CCl	$CH_2C\equiv C$-cycPr
264.	CCl	CCl	$CH_2C\equiv C$-2-furanyl
265.	CCl	CCl	$CH_2CH=CH$-cycPr
266.	CCl	CCl	$CH_2CH=CH$-2-furanyl

267.	CCl	CCl	$CH=CHCH_2$-cycPr
268.	CCl	CCl	$CH=CHCH_2$-2-furanyl
269.	CCl	CCl	$OCH_2C=C(CH_3)_2$
270.	CCl	CCl	*E*-$OCH_2C=CHCH_3$
271.	CCl	CCl	*Z*-$OCH_2C=CHCH_3$
272.	CCl	CCl	OCH_2CH_3
273.	CCl	CCl	$OCH_2CH_2CH_3$
274.	CCl	CCl	$OCH_2C=C(Cl)_2$
275.	CCl	CCl	$OCH_2C=CH_2$
276.	CCl	CCl	$OCH_2C\equiv CCH_3$
277.	CCl	CCl	$OCH_2CH_2CH_3$
278.	CCl	CCl	OCH_2-cycPr
279.	CCl	CCl	OCH_2-(1-CH_3-cycPr)
280.	CCl	CCl	OCH_2-cycBu
281.	CCl	CCl	OCH_2-(1-CH_3-cycBu)
282.	CCl	CCl	OCH_2-Phenyl
283.	CCl	CCl	OCH_2CH_2-cycPr
284.	CCl	CCl	OCH_2CH=cycPr
285.	CF	CH	C≡C-cycPr
286.	CF	CH	C≡C-(1-CH_3-cycPr)
287.	CF	CH	C≡C-iPr
288.	CF	CH	C≡C-nPr
289.	CF	CH	C≡C-Bu
290.	CF	CH	C≡C-iBu
291.	CF	CH	C≡C-tBu
292.	CF	CH	C≡C-Et
293.	CF	CH	C≡C-Me
294.	CF	CH	C≡C-Ph
295.	CF	CH	C≡C-2-Pyridyl
296.	CF	CH	C≡C-3-Pyridyl
297.	CF	CH	C≡C-4-Pyridyl
298.	CF	CH	C≡C-2-furanyl
299.	CF	CH	C≡C-3-furanyl
300.	CF	CH	C≡C-2-thienyl
301.	CF	CH	C≡C-3-thienyl
302.	CF	CH	CH=CH-cycPr

303.	CF	CH	CH=CH-iPr
304.	CF	CH	CH=CH-nPr
305.	CF	CH	CH=CH-Bu
306.	CF	CH	CH=CH-iBu
307.	CF	CH	CH=CH-tBu
308.	CF	CH	CH=CH-Et
309.	CF	CH	CH=CH-Me
310.	CF	CH	CH=CH-Ph
311.	CF	CH	CH=CH-2-Pyridyl
312.	CF	CH	CH=CH-3-Pyridyl
313.	CF	CH	CH=CH-4-Pyridyl
314.	CF	CH	CH=CH-2-furanyl
315.	CF	CH	CH=CH-3-furanyl
316.	CF	CH	CH=CH-2-thienyl
317.	CF	CH	CH=CH-3-thienyl
318.	CF	CH	$CH_2CH_2CH_2CH_2CH_3$
319.	CF	CH	$CH_2CH_2CH(CH_3)_2$
320.	CF	CH	$CH_2CH_2CH_2CH_3$
321.	CF	CH	$CH_2CH_2CH_3$
322.	CF	CH	CH_2CH_2-cycPr
323.	CF	CH	CH_2CH_2-(1-CH_3-cycPr)
324.	CF	CH	CH_2CH_2-tBu
325.	CF	CH	CH_2CH_2-cycBu
326.	CF	CH	CH_2CH_2-(1-CH_3-cycBu)
327.	CF	CH	CH_2CH_2-2-Pyridyl
328.	CF	CH	CH_2CH_2-3-Pyridyl
329.	CF	CH	CH_2CH_2-4-Pyridyl
330.	CF	CH	CH_2CH_2-2-furanyl
331.	CF	CH	CH_2CH_2-3-furanyl
332.	CF	CH	CH_2CH_2-2-thienyl
333.	CF	CH	CH_2CH_2-3-thienyl
334.	CF	CH	$CH_2C\equiv C$-cycPr
335.	CF	CH	$CH_2C\equiv C$-2-furanyl
336.	CF	CH	$CH_2CH=CH$-cycPr
337.	CF	CH	$CH_2CH=CH$-2-furanyl
338.	CF	CH	$CH=CHCH_2$-cycPr
339.	CF	CH	$CH=CHCH_2$-2-furanyl
340.	CF	CH	$OCH_2C=C(CH_3)_2$

341.	CF	CH	*E*-$OCH_2C{=}CHCH_3$
342.	CF	CH	*Z*-$OCH_2C{=}CHCH_3$
343.	CF	CH	OCH_2CH_3
344.	CF	CH	$OCH_2CH_2CH_3$
345.	CF	CH	$OCH_2C{=}C(Cl)_2$
346.	CF	CH	$OCH_2C{=}CH_2$
347.	CF	CH	$OCH_2C{\equiv}CCH_3$
348.	CF	CH	$OCH_2CH_2CH_3$
349.	CF	CH	OCH_2-cycPr
350.	CF	CH	OCH_2-(1-CH_3-cycPr)
351.	CF	CH	OCH_2-cycBu
352.	CF	CH	OCH_2-(1-CH_3-cycBu)
353.	CF	CH	OCH_2-Phenyl
354.	CF	CH	OCH_2CH_2-cycPr
355.	CF	CH	$OCH_2CH{=}$cycPr
356.	CH	CF	C≡C-cycPr
357.	CH	CF	C≡C-(1-CH_3-cycPr)
358.	CH	CF	C≡C-iPr
359.	CH	CF	C≡C-nPr
360.	CH	CF	C≡C-Bu
361.	CH	CF	C≡C-iBu
362.	CH	CF	C≡C-tBu
363.	CH	CF	C≡C-Et
364.	CH	CF	C≡C-Me
365.	CH	CF	C≡C-Ph
366.	CH	CF	C≡C-2-Pyridyl
367.	CH	CF	C≡C-3-Pyridyl
368.	CH	CF	C≡C-4-Pyridyl
369.	CH	CF	C≡C-2-furanyl
370.	CH	CF	C≡C-3-furanyl
371.	CH	CF	C≡C-2-thienyl
372.	CH	CF	C≡C-3-thienyl
373.	CH	CF	CH=CH-cycPr
374.	CH	CF	CH=CH-iPr
375.	CH	CF	CH=CH-nPr
376.	CH	CF	CH=CH-Bu
377.	CH	CF	CH=CH-iBu

378.	CH	CF	CH=CH-tBu
379.	CH	CF	CH=CH-Et
380.	CH	CF	CH=CH-Me
381.	CH	CF	CH=CH-Ph
382.	CH	CF	CH=CH-2-Pyridyl
383.	CH	CF	CH=CH-3-Pyridyl
384.	CH	CF	CH=CH-4-Pyridyl
385.	CH	CF	CH=CH-2-furanyl
386.	CH	CF	CH=CH-3-furanyl
387.	CH	CF	CH=CH-2-thienyl
388.	CH	CF	CH=CH-3-thienyl
389.	CH	CF	$CH_2CH_2CH_2CH_2CH_3$
390.	CH	CF	$CH_2CH_2CH(CH_3)_2$
391.	CH	CF	$CH_2CH_2CH_2CH_3$
392.	CH	CF	$CH_2CH_2CH_3$
393.	CH	CF	CH_2CH_2-cycPr
394.	CH	CF	CH_2CH_2-(1-CH_3-cycPr)
395.	CH	CF	CH_2CH_2-tBu
396.	CH	CF	CH_2CH_2-cycBu
397.	CH	CF	CH_2CH_2-(1-CH_3-cycBu)
398.	CH	CF	CH_2CH_2-2-Pyridyl
399.	CH	CF	CH_2CH_2-3-Pyridyl
400.	CH	CF	CH_2CH_2-4-Pyridyl
401.	CH	CF	CH_2CH_2-2-furanyl
402.	CH	CF	CH_2CH_2-3-furanyl
403.	CH	CF	CH_2CH_2-2-thienyl
404.	CH	CF	CH_2CH_2-3-thienyl
405.	CH	CF	$CH_2C\equiv C$-cycPr
406.	CH	CF	$CH_2C\equiv C$-2-furanyl
407.	CH	CF	$CH_2CH=CH$-cycPr
408.	CH	CF	$CH_2CH=CH$-2-furanyl
409.	CH	CF	$CH=CHCH_2$-cycPr
410.	CH	CF	$CH=CHCH_2$-2-furanyl
411.	CH	CF	$OCH_2C=C(CH_3)_2$
412.	CH	CF	*E*-$OCH_2C=CHCH_3$
413.	CH	CF	*Z*-$OCH_2C=CHCH_3$
414.	CH	CF	OCH_2CH_3
415.	CH	CF	$OCH_2CH_2CH_3$

416.	CH	CF	$OCH_2C=C(Cl)_2$
417.	CH	CF	$OCH_2C=CH_2$
418.	CH	CF	$OCH_2C\equiv CCH_3$
419.	CH	CF	$OCH_2CH_2CH_3$
420.	CH	CF	OCH_2-cycPr
421.	CH	CF	OCH_2-(1-CH_3-cycPr)
422.	CH	CF	OCH_2-cycBu
423.	CH	CF	OCH_2-(1-CH_3-cycBu)
424.	CH	CF	OCH_2-Phenyl
425.	CH	CF	OCH_2CH_2-cycPr
426.	CH	CF	OCH_2CH=cycPr
427.	CF	CF	C≡C-cycPr
428.	CF	CF	C≡C-(1-CH_3-cycPr)
429.	CF	CF	C≡C-iPr
430.	CF	CF	C≡C-nPr
431.	CF	CF	C≡C-Bu
432.	CF	CF	C≡C-iBu
433.	CF	CF	C≡C-tBu
434.	CF	CF	C≡C-Et
435.	CF	CF	C≡C-Me
436.	CF	CF	C≡C-Ph
437.	CF	CF	C≡C-2-Pyridyl
438.	CF	CF	C≡C-3-Pyridyl
439.	CF	CF	C≡C-4-Pyridyl
440.	CF	CF	C≡C-2-furanyl
441.	CF	CF	C≡C-3-furanyl
442.	CF	CF	C≡C-2-thienyl
443.	CF	CF	C≡C-3-thienyl
444.	CF	CF	CH=CH-cycPr
445.	CF	CF	CH=CH-iPr
446.	CF	CF	CH=CH-nPr
447.	CF	CF	CH=CH-Bu
448.	CF	CF	CH=CH-iBu
449.	CF	CF	CH=CH-tBu
450.	CF	CF	CH=CH-Et
451.	CF	CF	CH=CH-Me
452.	CF	CF	CH=CH-Ph
453.	CF	CF	CH=CH-2-Pyridyl

454.	CF	CF	CH=CH-3-Pyridyl
455.	CF	CF	CH=CH-4-Pyridyl
456.	CF	CF	CH=CH-2-furanyl
457.	CF	CF	CH=CH-3-furanyl
458.	CF	CF	CH=CH-2-thienyl
459.	CF	CF	CH=CH-3-thienyl
460.	CF	CF	$CH_2CH_2CH_2CH_2CH_3$
461.	CF	CF	$CH_2CH_2CH(CH_3)_2$
462.	CF	CF	$CH_2CH_2CH_2CH_3$
463.	CF	CF	$CH_2CH_2CH_3$
464.	CF	CF	CH_2CH_2-cycPr
465.	CF	CF	CH_2CH_2-(1-CH_3-cycPr)
466.	CF	CF	CH_2CH_2-tBu
467.	CF	CF	CH_2CH_2-cycBu
468.	CF	CF	CH_2CH_2-(1-CH_3-cycBu)
469.	CF	CF	CH_2CH_2-2-Pyridyl
470.	CF	CF	CH_2CH_2-3-Pyridyl
471.	CF	CF	CH_2CH_2-4-Pyridyl
472.	CF	CF	CH_2CH_2-2-furanyl
473.	CF	CF	CH_2CH_2-3-furanyl
474.	CF	CF	CH_2CH_2-2-thienyl
475.	CF	CF	CH_2CH_2-3-thienyl
476.	CF	CF	$CH_2C{\equiv}C$-cycPr
477.	CF	CF	$CH_2C{\equiv}C$-2-furanyl
478.	CF	CF	$CH_2CH{=}CH$-cycPr
479.	CF	CF	$CH_2CH{=}CH$-2-furanyl
480.	CF	CF	$CH{=}CHCH_2$-cycPr
481.	CF	CF	$CH{=}CHCH_2$-2-furanyl
482.	CF	CF	$OCH_2C{=}C(CH_3)_2$
483.	CF	CF	*E*-$OCH_2C{=}CHCH_3$
484.	CF	CF	*Z*-$OCH_2C{=}CHCH_3$
485.	CF	CF	OCH_2CH_3
486.	CF	CF	$OCH_2CH_2CH_3$
487.	CF	CF	$OCH_2C{=}C(Cl)_2$
488.	CF	CF	$OCH_2C{=}CH_2$
489.	CF	CF	$OCH_2C{\equiv}CCH_3$
490.	CF	CF	$OCH_2CH_2CH_3$

491.	CF	CF	OCH_2-cycPr
492.	CF	CF	OCH_2-(1-CH_3-cycPr)
493.	CF	CF	OCH_2-cycBu
494.	CF	CF	OCH_2-(1-CH_3-cycBu)
495.	CF	CF	OCH_2-Phenyl
496.	CF	CF	OCH_2CH_2-cycPr
497.	CF	CF	OCH_2CH=cycPr
498.	CCl	CF	C≡C-cycPr
499.	CCl	CF	C≡C-(1-CH_3-cycPr)
500.	CCl	CF	C≡C-iPr
501.	CCl	CF	C≡C-nPr
502.	CCl	CF	C≡C-Bu
503.	CCl	CF	C≡C-iBu
504.	CCl	CF	C≡C-tBu
505.	CCl	CF	C≡C-Et
506.	CCl	CF	C≡C-Me
507.	CCl	CF	C≡C-Ph
508.	CCl	CF	C≡C-2-Pyridyl
509.	CCl	CF	C≡C-3-Pyridyl
510.	CCl	CF	C≡C-4-Pyridyl
511.	CCl	CF	C≡C-2-furanyl
512.	CCl	CF	C≡C-3-furanyl
513.	CCl	CF	C≡C-2-thienyl
514.	CCl	CF	C≡C-3-thienyl
515.	CCl	CF	CH=CH-cycPr
516.	CCl	CF	CH=CH-iPr
517.	CCl	CF	CH=CH-nPr
518.	CCl	CF	CH=CH-Bu
519.	CCl	CF	CH=CH-iBu
520.	CCl	CF	CH=CH-tBu
521.	CCl	CF	CH=CH-Et
522.	CCl	CF	CH=CH-Me
523.	CCl	CF	CH=CH-Ph
524.	CCl	CF	CH=CH-2-Pyridyl
525.	CCl	CF	CH=CH-3-Pyridyl
526.	CCl	CF	CH=CH-4-Pyridyl
527.	CCl	CF	CH=CH-2-furanyl
528.	CCl	CF	CH=CH-3-furanyl
529.	CCl	CF	CH=CH-2-thienyl

530.	CCl	CF	CH=CH-3-thienyl
531.	CCl	CF	$CH_2CH_2CH_2CH_2CH_3$
532.	CCl	CF	$CH_2CH_2CH(CH_3)_2$
533.	CCl	CF	$CH_2CH_2CH_2CH_3$
534.	CCl	CF	$CH_2CH_2CH_3$
535.	CCl	CF	CH_2CH_2-cycPr
536.	CCl	CF	CH_2CH_2-(1-CH_3-cycPr)
537.	CCl	CF	CH_2CH_2-tBu
538.	CCl	CF	CH_2CH_2-cycBu
539.	CCl	CF	CH_2CH_2-(1-CH_3-cycBu)
540.	CCl	CF	CH_2CH_2-2-Pyridyl
541.	CCl	CF	CH_2CH_2-3-Pyridyl
542.	CCl	CF	CH_2CH_2-4-Pyridyl
543.	CCl	CF	CH_2CH_2-2-furanyl
544.	CCl	CF	CH_2CH_2-3-furanyl
545.	CCl	CF	CH_2CH_2-2-thienyl
546.	CCl	CF	CH_2CH_2-3-thienyl
547.	CCl	CF	$CH_2C\equiv C$-cycPr
548.	CCl	CF	$CH_2C\equiv C$-2-furanyl
549.	CCl	CF	$CH_2CH=CH$-cycPr
550.	CCl	CF	$CH_2CH=CH$-2-furanyl
551.	CCl	CF	$CH=CHCH_2$-cycPr
552.	CCl	CF	$CH=CHCH_2$-2-furanyl
553.	CCl	CF	$OCH_2C=C(CH_3)_2$
554.	CCl	CF	*E*-$OCH_2C=CHCH_3$
555.	CCl	CF	*Z*-$OCH_2C=CHCH_3$
556.	CCl	CF	OCH_2CH_3
557.	CCl	CF	$OCH_2CH_2CH_3$
558.	CCl	CF	$OCH_2C=C(Cl)_2$
559.	CCl	CF	$OCH_2C=CH_2$
560.	CCl	CF	$OCH_2C\equiv CCH_3$
561.	CCl	CF	$OCH_2CH_2CH_3$
562.	CCl	CF	OCH_2-cycPr
563.	CCl	CF	OCH_2-(1-CH_3-cycPr)
564.	CCl	CF	OCH_2-cycBu
565.	CCl	CF	OCH_2-(1-CH_3-cycBu)
566.	CCl	CF	OCH_2-Phenyl

567.	CCl	CF	OCH_2CH_2-cycPr
568.	CCl	CF	OCH_2CH=cycPr
569.	CF	CCl	C≡C-cycPr
570.	CF	CCl	C≡C-(1-CH_3-cycPr)
571.	CF	CCl	C≡C-iPr
572.	CF	CCl	C≡C-nPr
573.	CF	CCl	C≡C-Bu
574.	CF	CCl	C≡C-iBu
575.	CF	CCl	C≡C-tBu
576.	CF	CCl	C≡C-Et
577.	CF	CCl	C≡C-Me
578.	CF	CCl	C≡C-Ph
579.	CF	CCl	C≡C-2-Pyridyl
580.	CF	CCl	C≡C-3-Pyridyl
581.	CF	CCl	C≡C-4-Pyridyl
582.	CF	CCl	C≡C-2-furanyl
583.	CF	CCl	C≡C-3-furanyl
584.	CF	CCl	C≡C-2-thienyl
585.	CF	CCl	C≡C-3-thienyl
586.	CF	CCl	CH=CH-cycPr
587.	CF	CCl	CH=CH-iPr
588.	CF	CCl	CH=CH-nPr
589.	CF	CCl	CH=CH-Bu
590.	CF	CCl	CH=CH-iBu
591.	CF	CCl	CH=CH-tBu
592.	CF	CCl	CH=CH-Et
593.	CF	CCl	CH=CH-Me
594.	CF	CCl	CH=CH-Ph
595.	CF	CCl	CH=CH-2-Pyridyl
596.	CF	CCl	CH=CH-3-Pyridyl
597.	CF	CCl	CH=CH-4-Pyridyl
598.	CF	CCl	CH=CH-2-furanyl
599.	CF	CCl	CH=CH-3-furanyl
600.	CF	CCl	CH=CH-2-thienyl
601.	CF	CCl	CH=CH-3-thienyl
602.	CF	CCl	$CH_2CH_2CH_2CH_2CH_3$
603.	CF	CCl	$CH_2CH_2CH(CH_3)_2$
604.	CF	CCl	$CH_2CH_2CH_2CH_3$
605.	CF	CCl	$CH_2CH_2CH_3$

606.	CF	CCl	CH_2CH_2-cycPr
607.	CF	CCl	CH_2CH_2-(1-CH_3-cycPr)
608.	CF	CCl	CH_2CH_2-tBu
609.	CF	CCl	CH_2CH_2-cycBu
610.	CF	CCl	CH_2CH_2-(1-CH_3-cycBu)
611.	CF	CCl	CH_2CH_2-2-Pyridyl
612.	CF	CCl	CH_2CH_2-3-Pyridyl
613.	CF	CCl	CH_2CH_2-4-Pyridyl
614.	CF	CCl	CH_2CH_2-2-furanyl
615.	CF	CCl	CH_2CH_2-3-furanyl
616.	CF	CCl	CH_2CH_2-2-thienyl
617.	CF	CCl	CH_2CH_2-3-thienyl
618.	CF	CCl	$CH_2C{\equiv}C$-cycPr
619.	CF	CCl	$CH_2C{\equiv}C$-2-furanyl
620.	CF	CCl	$CH_2CH{=}CH$-cycPr
621.	CF	CCl	$CH_2CH{=}CH$-2-furanyl
622.	CF	CCl	$CH{=}CHCH_2$-cycPr
623.	CF	CCl	$CH{=}CHCH_2$-2-furanyl
624.	CF	CCl	$OCH_2C{=}C(CH_3)_2$
625.	CF	CCl	*E*-$OCH_2C{=}CHCH_3$
626.	CF	CCl	*Z*-$OCH_2C{=}CHCH_3$
627.	CF	CCl	OCH_2CH_3
628.	CF	CCl	$OCH_2CH_2CH_3$
629.	CF	CCl	$OCH_2C{=}C(Cl)_2$
630.	CF	CCl	$OCH_2C{=}CH_2$
631.	CF	CCl	$OCH_2C{\equiv}CCH_3$
632.	CF	CCl	$OCH_2CH_2CH_3$
633.	CF	CCl	OCH_2-cycPr
634.	CF	CCl	OCH_2-(1-CH_3-cycPr)
635.	CF	CCl	OCH_2-cycBu
636.	CF	CCl	OCH_2-(1-CH_3-cycBu)
637.	CF	CCl	OCH_2-Phenyl
638.	CF	CCl	OCH_2CH_2-cycPr
639.	CF	CCl	$OCH_2CH{=}$cycPr
640.	C(OMe)	CH	$C{\equiv}C$-cycPr
641.	C(OMe)	CH	$C{\equiv}C$-(1-CH_3-cycPr)

642.	C(OMe)	CH	C≡C-iPr
643.	C(OMe)	CH	C≡C-nPr
644.	C(OMe)	CH	C≡C-Bu
645.	C(OMe)	CH	C≡C-iBu
646.	C(OMe)	CH	C≡C-tBu
647.	C(OMe)	CH	C≡C-Et
648.	C(OMe)	CH	C≡C-Me
649.	C(OMe)	CH	C≡C-Ph
650.	C(OMe)	CH	C≡C-2-Pyridyl
651.	C(OMe)	CH	C≡C-3-Pyridyl
652.	C(OMe)	CH	C≡C-4-Pyridyl
653.	C(OMe)	CH	C≡C-2-furanyl
654.	C(OMe)	CH	C≡C-3-furanyl
655.	C(OMe)	CH	C≡C-2-thienyl
656.	C(OMe)	CH	C≡C-3-thienyl
657.	C(OMe)	CH	CH=CH-cycPr
658.	C(OMe)	CH	CH=CH-iPr
659.	C(OMe)	CH	CH=CH-nPr
660.	C(OMe)	CH	CH=CH-Bu
661.	C(OMe)	CH	CH=CH-iBu
662.	C(OMe)	CH	CH=CH-tBu
663.	C(OMe)	CH	CH=CH-Et
664.	C(OMe)	CH	CH=CH-Me
665.	C(OMe)	CH	CH=CH-Ph
666.	C(OMe)	CH	CH=CH-2-Pyridyl
667.	C(OMe)	CH	CH=CH-3-Pyridyl
668.	C(OMe)	CH	CH=CH-4-Pyridyl
669.	C(OMe)	CH	CH=CH-2-furanyl
670.	C(OMe)	CH	CH=CH-3-furanyl
671.	C(OMe)	CH	CH=CH-2-thienyl
672.	C(OMe)	CH	CH=CH-3-thienyl
673.	C(OMe)	CH	$CH_2CH_2CH_2CH_2CH_3$
674.	C(OMe)	CH	$CH_2CH_2CH(CH_3)_2$
675.	C(OMe)	CH	$CH_2CH_2CH_2CH_3$
676.	C(OMe)	CH	$CH_2CH_2CH_3$
677.	C(OMe)	CH	CH_2CH_2-cycPr
678.	C(OMe)	CH	CH_2CH_2-(1-CH_3-cycPr)
679.	C(OMe)	CH	CH_2CH_2-tBu
680.	C(OMe)	CH	CH_2CH_2-cycBu

681.	C(OMe)	CH	CH_2CH_2-(1-CH_3-cycBu)
682.	C(OMe)	CH	CH_2CH_2-2-Pyridyl
683.	C(OMe)	CH	CH_2CH_2-3-Pyridyl
684.	C(OMe)	CH	CH_2CH_2-4-Pyridyl
685.	C(OMe)	CH	CH_2CH_2-2-furanyl
686.	C(OMe)	CH	CH_2CH_2-3-furanyl
687.	C(OMe)	CH	CH_2CH_2-2-thienyl
688.	C(OMe)	CH	CH_2CH_2-3-thienyl
689.	C(OMe)	CH	$CH_2C{\equiv}C$-cycPr
690.	C(OMe)	CH	$CH_2C{\equiv}C$-2-furanyl
691.	C(OMe)	CH	$CH_2CH{=}CH$-cycPr
692.	C(OMe)	CH	$CH_2CH{=}CH$-2-furanyl
693.	C(OMe)	CH	$CH{=}CHCH_2$-cycPr
694.	C(OMe)	CH	$CH{=}CHCH_2$-2-furanyl
695.	C(OMe)	CH	$OCH_2C{=}C(CH_3)_2$
696.	C(OMe)	CH	*E*-$OCH_2C{=}CHCH_3$
697.	C(OMe)	CH	*Z*-$OCH_2C{=}CHCH_3$
698.	C(OMe)	CH	OCH_2CH_3
699.	C(OMe)	CH	$OCH_2CH_2CH_3$
700.	C(OMe)	CH	$OCH_2C{=}C(Cl)_2$
701.	C(OMe)	CH	$OCH_2C{=}CH_2$
702.	C(OMe)	CH	$OCH_2C{\equiv}CCH_3$
703.	C(OMe)	CH	$OCH_2CH_2CH_3$
704.	C(OMe)	CH	OCH_2-cycPr
705.	C(OMe)	CH	OCH_2-(1-CH_3-cycPr)
706.	C(OMe)	CH	OCH_2-cycBu
707.	C(OMe)	CH	OCH_2-(1-CH_3-cycBu)
708.	C(OMe)	CH	OCH_2-Phenyl
709.	C(OMe)	CH	OCH_2CH_2-cycPr
710.	C(OMe)	CH	$OCH_2CH{=}$cycPr
711.	CH	C(OMe)	$C{\equiv}C$-cycPr
712.	CH	C(OMe)	$C{\equiv}C$-(1-CH_3-cycPr)
713.	CH	C(OMe)	$C{\equiv}C$-iPr
714.	CH	C(OMe)	$C{\equiv}C$-nPr
715.	CH	C(OMe)	$C{\equiv}C$-Bu
716.	CH	C(OMe)	$C{\equiv}C$-iBu

717.	CH	C(OMe)	C≡C-tBu
718.	CH	C(OMe)	C≡C-Et
719.	CH	C(OMe)	C≡C-Me
720.	CH	C(OMe)	C≡C-Ph
721.	CH	C(OMe)	C≡C-2-Pyridyl
722.	CH	C(OMe)	C≡C-3-Pyridyl
723.	CH	C(OMe)	C≡C-4-Pyridyl
724.	CH	C(OMe)	C≡C-2-furanyl
725.	CH	C(OMe)	C≡C-3-furanyl
726.	CH	C(OMe)	C≡C-2-thienyl
727.	CH	C(OMe)	C≡C-3-thienyl
728.	CH	C(OMe)	CH=CH-cycPr
729.	CH	C(OMe)	CH=CH-iPr
730.	CH	C(OMe)	CH=CH-nPr
731.	CH	C(OMe)	CH=CH-Bu
732.	CH	C(OMe)	CH=CH-iBu
733.	CH	C(OMe)	CH=CH-tBu
734.	CH	C(OMe)	CH=CH-Et
735.	CH	C(OMe)	CH=CH-Me
736.	CH	C(OMe)	CH=CH-Ph
737.	CH	C(OMe)	CH=CH-2-Pyridyl
738.	CH	C(OMe)	CH=CH-3-Pyridyl
739.	CH	C(OMe)	CH=CH-4-Pyridyl
740.	CH	C(OMe)	CH=CH-2-furanyl
741.	CH	C(OMe)	CH=CH-3-furanyl
742.	CH	C(OMe)	CH=CH-2-thienyl
743.	CH	C(OMe)	CH=CH-3-thienyl
744.	CH	C(OMe)	$CH_2CH_2CH_2CH_2CH_3$
745.	CH	C(OMe)	$CH_2CH_2CH(CH_3)_2$
746.	CH	C(OMe)	$CH_2CH_2CH_2CH_3$
747.	CH	C(OMe)	$CH_2CH_2CH_3$
748.	CH	C(OMe)	CH_2CH_2-cycPr
749.	CH	C(OMe)	CH_2CH_2-(1-CH_3-cycPr)
750.	CH	C(OMe)	CH_2CH_2-tBu
751.	CH	C(OMe)	CH_2CH_2-cycBu
752.	CH	C(OMe)	CH_2CH_2-(1-CH_3-cycBu)
753.	CH	C(OMe)	CH_2CH_2-2-Pyridyl
754.	CH	C(OMe)	CH_2CH_2-3-Pyridyl
755.	CH	C(OMe)	CH_2CH_2-4-Pyridyl

756.	CH	C(OMe)	CH_2CH_2-2-furanyl
757.	CH	C(OMe)	CH_2CH_2-3-furanyl
758.	CH	C(OMe)	CH_2CH_2-2-thienyl
759.	CH	C(OMe)	CH_2CH_2-3-thienyl
760.	CH	C(OMe)	$CH_2C{\equiv}C$-cycPr
761.	CH	C(OMe)	$CH_2C{\equiv}C$-2-furanyl
762.	CH	C(OMe)	$CH_2CH{=}CH$-cycPr
763.	CH	C(OMe)	$CH_2CH{=}CH$-2-furanyl
764.	CH	C(OMe)	$CH{=}CHCH_2$-cycPr
765.	CH	C(OMe)	$CH{=}CHCH_2$-2-furanyl
766.	CH	C(OMe)	$OCH_2C{=}C(CH_3)_2$
767.	CH	C(OMe)	*E*-$OCH_2C{=}CHCH_3$
768.	CH	C(OMe)	*Z*-$OCH_2C{=}CHCH_3$
769.	CH	C(OMe)	OCH_2CH_3
770.	CH	C(OMe)	$OCH_2CH_2CH_3$
771.	CH	C(OMe)	$OCH_2C{=}C(Cl)_2$
772.	CH	C(OMe)	$OCH_2C{=}CH_2$
773.	CH	C(OMe)	$OCH_2C{\equiv}CCH_3$
774.	CH	C(OMe)	$OCH_2CH_2CH_3$
775.	CH	C(OMe)	OCH_2-cycPr
776.	CH	C(OMe)	OCH_2-(1-CH_3-cycPr)
777.	CH	C(OMe)	OCH_2-cycBu
778.	CH	C(OMe)	OCH_2-(1-CH_3-cycBu)
779.	CH	C(OMe)	OCH_2-Phenyl
780.	CH	C(OMe)	OCH_2CH_2-cycPr
781.	CH	C(OMe)	$OCH_2CH{=}$cycPr
782.	-COCH2OC-		C≡C-cycPr
783.	-COCH2OC-		C≡C-(1-CH_3-cycPr)
784.	-COCH2OC-		C≡C-iPr
785.	-COCH2OC-		C≡C-nPr
786.	-COCH2OC-		C≡C-Bu
787.	-COCH2OC-		C≡C-iBu
788.	-COCH2OC-		C≡C-tBu
789.	-COCH2OC-		C≡C-Et
790.	-COCH2OC-		C≡C-Me
791.	-COCH2OC-		C≡C-Ph

792.	-COCH2OC-	C≡C-2-Pyridyl
793.	-COCH2OC-	C≡C-3-Pyridyl
794.	-COCH2OC-	C≡C-4-Pyridyl
795.	-COCH2OC-	C≡C-2-furanyl
796.	-COCH2OC-	C≡C-3-furanyl
797.	-COCH2OC-	C≡C-2-thienyl
798.	-COCH2OC-	C≡C-3-thienyl
799.	-COCH2OC-	CH=CH-cycPr
800.	-COCH2OC-	CH=CH-iPr
801.	-COCH2OC-	CH=CH-nPr
802.	-COCH2OC-	CH=CH-Bu
803.	-COCH2OC-	CH=CH-iBu
804.	-COCH2OC-	CH=CH-tBu
805.	-COCH2OC-	CH=CH-Et
806.	-COCH2OC-	CH=CH-Me
807.	-COCH2OC-	CH=CH-Ph
808.	-COCH2OC-	CH=CH-2-Pyridyl
809.	-COCH2OC-	CH=CH-3-Pyridyl
810.	-COCH2OC-	CH=CH-4-Pyridyl
811.	-COCH2OC-	CH=CH-2-furanyl
812.	-COCH2OC-	CH=CH-3-furanyl
813.	-COCH2OC-	CH=CH-2-thienyl
814.	-COCH2OC-	CH=CH-3-thienyl
815.	-COCH2OC-	$CH_2CH_2CH_2CH_2CH_3$
816.	-COCH2OC-	$CH_2CH_2CH(CH_3)_2$
817.	-COCH2OC-	$CH_2CH_2CH_2CH_3$
818.	-COCH2OC-	$CH_2CH_2CH_3$
819.	-COCH2OC-	CH_2CH_2-cycPr
820.	-COCH2OC-	CH_2CH_2-(1-CH_3-cycPr)
821.	-COCH2OC-	CH_2CH_2-tBu
822.	-COCH2OC-	CH_2CH_2-cycBu
823.	-COCH2OC-	CH_2CH_2-(1-CH_3-cycBu)
824.	-COCH2OC-	CH_2CH_2-2-Pyridyl
825.	-COCH2OC-	CH_2CH_2-3-Pyridyl
826.	-COCH2OC-	CH_2CH_2-4-Pyridyl
827.	-COCH2OC-	CH_2CH_2-2-furanyl
828.	-COCH2OC-	CH_2CH_2-3-furanyl
829.	-COCH2OC-	CH_2CH_2-2-thienyl
830.	-COCH2OC-	CH_2CH_2-3-thienyl

831.	-COCH2OC-	$CH_2C{\equiv}C$-cycPr
832.	-COCH2OC-	$CH_2C{\equiv}C$-2-furanyl
833.	-COCH2OC-	$CH_2CH{=}CH$-cycPr
834.	-COCH2OC-	$CH_2CH{=}CH$-2-furanyl
835.	-COCH2OC-	$CH{=}CHCH_2$-cycPr
836.	-COCH2OC-	$CH{=}CHCH_2$-2-furanyl
837.	-COCH2OC-	$OCH_2C{=}C(CH_3)_2$
838.	-COCH2OC-	*E*-$OCH_2C{=}CHCH_3$
839.	-COCH2OC-	*Z*-$OCH_2C{=}CHCH_3$
840.	-COCH2OC-	OCH_2CH_3
841.	-COCH2OC-	$OCH_2CH_2CH_3$
842.	-COCH2OC-	$OCH_2C{=}C(Cl)_2$
843.	-COCH2OC-	$OCH_2C{=}CH_2$
844.	-COCH2OC-	$OCH_2C{\equiv}CCH_3$
845.	-COCH2OC-	$OCH_2CH_2CH_3$
846.	-COCH2OC-	OCH_2-cycPr
847.	-COCH2OC-	OCH_2-(1-CH_3-cycPr)
848.	-COCH2OC-	OCH_2-cycBu
849.	-COCH2OC-	OCH_2-(1-CH_3-cycBu)
850.	-COCH2OC-	OCH_2-Phenyl
851.	-COCH2OC-	OCH_2CH_2-cycPr
852.	-COCH2OC-	$OCH_2CH{=}$cycPr

*Unless otherwise noted, stereochemistry is (+/-) and in R^2, all double bonds are cis and trans.

Utility

The compounds of this invention possess reverse transcriptase inhibitory activity, in particular, HIV inhibitory efficacy. The compounds of formula (I) possess HIV reverse transcriptase inhibitory activity and are therefore useful as antiviral agents for the treatment of HIV infection and associated diseases. The compounds of formula (I) possess HIV reverse transcriptase inhibitory activity and are effective as inhibitors of HIV growth. The ability of the compounds of the present invention to inhibit viral growth or infectivity is demonstrated in standard assay of viral growth or infectivity, for example, using the assay described below.

The compounds of formula (I) of the present invention are also useful for the inhibition of HIV in an *ex vivo* sample containing HIV or expected to be exposed to HIV. Thus, the compounds of the present invention may be used to inhibit HIV present in a body fluid sample (for example, a serum or semen sample) which contains or is suspected to contain or be exposed to HIV.

The compounds provided by this invention are also useful as standard or reference compounds for use in tests or assays for determining the ability of an agent to inhibit viral clone replication and/or HIV reverse transcriptase, for example in a pharmaceutical research program. Thus, the compounds of the present invention may be used as a control or reference compound in such assays and as a quality control standard. The compounds of the present invention may be provided in a commercial kit or container for use as such standard or reference compound.

Since the compounds of the present invention exhibit specificity for HIV reverse transcriptase, the compounds of the present invention may also be useful as diagnostic reagents in diagnostic assays for the detection of HIV reverse transcriptase. Thus, inhibition of the reverse transcriptase activity in an assay (such as the assays

described herein) by a compound of the present invention would be indicative of the presence of HIV reverse transcriptase and HIV virus.

As used herein "µg" denotes microgram, "mg" denotes milligram, "g" denotes gram, "µL" denotes microliter, "mL" denotes milliliter, "L" denotes liter, "nM" denotes nanomolar, "µM" denotes micromolar, "mM" denotes millimolar, "M" denotes molar and "nm" denotes nanometer. "Sigma" stands for the Sigma-Aldrich Corp. of St. Louis, MO.

HIV RNA Assay

DNA Plasmids and *in vitro* RNA transcripts:

Plasmid pDAB 72 containing both gag and pol sequences of BH10 (bp 113-1816) cloned into PTZ 19R was prepared according to Erickson-Viitanen et al. *AIDS Research and Human Retroviruses* **1989**, *5*, 577. The plasmid was linearized with Bam HI prior to the generation of *in vitro* RNA transcripts using the Riboprobe Gemini system II kit (Promega) with T7 RNA polymerase. Synthesized RNA was purified by treatment with RNase free DNAse (Promega), phenol-chloroform extraction, and ethanol precipitation. RNA transcripts were dissolved in water, and stored at -70°C. The concentration of RNA was determined from the A_{260}.

Probes:

Biotinylated capture probes were purified by HPLC after synthesis on an Applied Biosystems (Foster City, CA) DNA synthesizer by addition of biotin to the 5' terminal end of the oligonucleotide, using the biotin-phosphoramidite reagent of Cocuzza, *Tet. Lett.* **1989**, *30*, 6287. The gag biotinylated capture probe (5-biotin-CTAGCTCCCTGCTTGCCCATACTA 3') was complementary to nucleotides 889-912 of HXB2 and the pol biotinylated capture probe (5'-biotin -CCCTATCATTTTTGGTTTCCAT 3') was complementary to nucleotides 2374-2395 of HXB2. Alkaline

phosphatase conjugated oligonucleotides used as reporter probes were prepared by Syngene (San Diego, CA.). The pol reporter probe (5' CTGTCTTACTTTGATAAAACCTC 3') was complementary to nucleotides 2403-2425 of HXB2. The gag reporter probe (5' CCCAGTATTTGTCTACAGCCTTCT 3') was complementary to nucleotides 950-973 of HXB2. All nucleotide positions are those of the GenBank Genetic Sequence Data Bank as accessed through the Genetics Computer Group Sequence Analysis Software Package (Devereau *Nucleic Acids Research* **1984**, *12*, 387). The reporter probes were prepared as 0.5 µM stocks in 2 x SSC (0.3 M NaCl, 0.03 M sodium citrate), 0.05 M Tris pH 8.8, 1 mg/mL BSA. The biotinylated capture probes were prepared as 100 µM stocks in water.

Streptavidin coated plates:

Streptavidin coated plates were obtained from Du Pont Biotechnology Systems (Boston, MA).

Cells and virus stocks:

MT-2 and MT-4 cells were maintained in RPMI 1640 supplemented with 5% fetal calf serum (FCS) for MT-2 cells or 10% FCS for MT-4 cells, 2 mM L-glutamine and 50 µg/mL gentamycin, all from Gibco. HIV-1 RF was propagated in MT-4 cells in the same medium. Virus stocks were prepared approximately 10 days after acute infection of MT-4 cells and stored as aliquots at -70°C. Infectious titers of HIV-1(RF) stocks were 1-3 x 10^7 PFU (plaque forming units)/mL as measured by plaque assay on MT-2 cells (see below). Each aliquot of virus stock used for infection was thawed only once.

For evaluation of antiviral efficacy, cells to be infected were subcultured one day prior to infection. On the day of infection, cells were resuspended at 5 x 10^5 cells/mL in RPMI 1640, 5% FCS for bulk infections or at 2 x

10^6/mL in Dulbecco's modified Eagles medium with 5% FCS for infection in microtiter plates. Virus was added and culture continued for 3 days at 37°C.

HIV RNA assay:

Cell lysates or purified RNA in 3 M or 5 M GED were mixed with 5 M GED and capture probe to a final guanidinium isothiocyanate concentration of 3 M and a final biotin oligonucleotide concentration of 30 nM. Hybridization was carried out in sealed U bottom 96 well tissue culture plates (Nunc or Costar) for 16-20 hours at 37°C. RNA hybridization reactions were diluted three-fold with deionized water to a final guanidinium isothiocyanate concentration of 1 M and aliquots (150 µL) were transferred to streptavidin coated microtiter plates wells. Binding of capture probe and capture probe-RNA hybrid to the immobilized streptavidin was allowed to proceed for 2 hours at room temperature, after which the plates were washed 6 times with DuPont ELISA plate wash buffer (phosphate buffered saline(PBS), 0.05% Tween 20.) A second hybridization of reporter probe to the immobilized complex of capture probe and hybridized target RNA was carried out in the washed streptavidin coated well by addition of 120 µl of a hybridization cocktail containing 4 X SSC, 0.66% Triton X 100, 6.66% deionized formamide, 1 mg/mL BSA and 5 nM reporter probe. After hybridization for one hour at 37°C, the plate was again washed 6 times. Immobilized alkaline phosphatase activity was detected by addition of 100 µL of 0.2 mM 4-methylumbelliferyl phosphate (MUBP, JBL Scientific) in buffer δ (2.5 M diethanolamine pH 8.9 (JBL Scientific), 10 mM $MgCl_2$, 5 mM zinc acetate dihydrate and 5 mM *N*-hydroxyethyl-ethylene-diamine-triacetic acid). The plates were incubated at 37°C. Fluorescence at 450 nM was measured using a microplate fluorometer (Dynateck) exciting at 365 nM.

Microplate based compound evaluation in HIV-1 infected MT-2 cells:

Compounds to be evaluated were dissolved in DMSO and diluted in culture medium to twice the highest concentration to be tested and a maximum DMSO concentration of 2%. Further three-fold serial dilutions of the compound in culture medium were performed directly in U bottom microtiter plates (Nunc). After compound dilution, MT-2 cells (50 µL) were added to a final concentration of 5×10^5 per mL (1×10^5 per well). Cells were incubated with compounds for 30 minutes at 37°C in a CO_2 incubator. For evaluation of antiviral potency, an appropriate dilution of HIV-1 (RF) virus stock (50 µL) was added to culture wells containing cells and dilutions of the test compounds. The final volume in each well was 200 µL. Eight wells per plate were left uninfected with 50 µL of medium added in place of virus, while eight wells were infected in the absence of any antiviral compound. For evaluation of compound toxicity, parallel plates were cultured without virus infection.

After 3 days of culture at 37°C in a humidified chamber inside a CO_2 incubator, all but 25 µL of medium/well was removed from the HIV infected plates. Thirty seven µL of 5 M GED containing biotinylated capture probe was added to the settled cells and remaining medium in each well to a final concentration of 3 M GED and 30 nM capture probe. Hybridization of the capture probe to HIV RNA in the cell lysate was carried out in the same microplate well used for virus culture by sealing the plate with a plate sealer (Costar), and incubating for 16-20 hrs in a 37°C incubator. Distilled water was then added to each well to dilute the hybridization reaction three-fold and 150 µL of this diluted mixture was transferred to a streptavidin coated microtiter plate. HIV RNA was quantitated as described above. A standard curve, prepared by adding known amounts of pDAB 72 *in vitro* RNA transcript to wells containing lysed uninfected

cells, was run on each microtiter plate in order to determine the amount of viral RNA made during the infection.

In order to standardize the virus inoculum used in the evaluation of compounds for antiviral activity, dilutions of virus were selected which resulted in an IC_{90} value (concentration of compound required to reduce the HIV RNA level by 90%) for dideoxycytidine (ddC) of 0.2 µg/mL. IC_{90} values of other antiviral compounds, both more and less potent than ddC, were reproducible using several stocks of HIV-1 (RF) when this procedure was followed. This concentration of virus corresponded to ~3 x 10^5 PFU (measured by plaque assay on MT-2 cells) per assay well and typically produced approximately 75% of the maximum viral RNA level achievable at any virus inoculum. For the HIV RNA assay, IC_{90} values were determined from the percent reduction of net signal (signal from infected cell samples minus signal from uninfected cell samples) in the RNA assay relative to the net signal from infected, untreated cells on the same culture plate (average of eight wells). Valid performance of individual infection and RNA assay tests was judged according to three criteria. It was required that the virus infection should result in an RNA assay signal equal to or greater than the signal generated from 2 ng of pDAB 72 *in vitro* RNA transcript. The IC_{90} for ddC, determined in each assay run, should be between 0.1 and 0.3 µg/mL. Finally, the plateau level of viral RNA produced by an effective reverse transcriptase inhibitor should be less than 10% of the level achieved in an uninhibited infection.

For antiviral potency tests, all manipulations in microtiter plates, following the initial addition of 2X concentrated compound solution to a single row of wells, were performed using a Perkin Elmer/Cetus ProPette.

Compounds tested in the above assay are considered to be active if they exhibit an IC_{90} of $\leq$20 µM. Preferred compounds of the present invention have IC_{90}'s of $\leq$5 µM.

More preferred compounds of the present invention have IC_{90}'s of ≤ 0.5 μM. Even more preferred compounds of the present invention have IC_{90}'s of ≤ 0.05 μM. Still more preferred compounds of the present invention have IC_{90}'s of ≤ 0.005 μM.

Using the methodology described above, a number of compounds of the present invention were found to exhibit an IC_{90} of ≤ 20 μM, thereby confirming the utility of the compounds of the present invention as effective HIV inhibitors.

Protein Binding and Mutant Resistance

In order to characterize NNRTI analogs for their clinical efficacy potential the effect of plasma proteins on antiviral potency and measurements of antiviral potency against wild type and mutant variants of HIV which carry amino acid changes in the known binding site for NNRTIs were examined. The rationale for this testing strategy is two fold:

1. Many drugs are extensively bound to plasma proteins. Although the binding affinity for most drugs for the major components of human plasma, namely, human serum albumin (HSA) or alpha-1-acid glycoprotein (AAG), is low, these major components are present in high concentration in the blood. Only free or unbound drug is available to cross the infected cell membrane for interaction with the target site (i.e., HIV-1 reverse transcriptase, HIV-1 RT). Therefore, the effect of added HSA+AAG on the antiviral potency in tissue culture more closely reflects the potency of a given compound in the clinical setting. The concentration of compound required for 90% inhibition of virus replication as measured in a sensitive viral RNA-based detection method is designated the IC90. The fold increase in apparent IC90 for test compounds in the presence or added levels of HSA and AAG that reflect *in vivo* concentrations (45 mg/ml HSA, 1 mg/ml AAG) was then calculated. The lower

the fold increase, the more compound will be available to interact with the target site.

2. The combination of the high rate of virus replication in the infected individual and the poor fidelity of the viral RT results in the production of a quasi-species or mixtures of HIV species in the infected individual. These species will include a majority wild type species, but also mutant variants of HIV and the proportion of a given mutant will reflect its relative fitness and replication rate. Because mutant variants including mutants with changes in the amino acid sequence of the viral RT likely pre-exist in the infected individual's quasi-species, the overall potency observed in the clinical setting will reflect the ability of a drug to inhibit not only wild type HIV-1, but mutant variants as well. We thus have constructed, in a known genetic background, mutant variants of HIV-1 which carry amino acid substitutions at positions thought to be involved in NNRTI binding, and measured the ability of test compounds to inhibit replication of these mutant viruses. The concentration of compound required for 90% inhibition of virus replication as measured in a sensitive viral RNA-based detection method is designated the IC90. It is desirable to have a compound which has high activity against a variety of mutants.

Dosage and Formulation

The antiviral compounds of this invention can be administered as treatment for viral infections by any means that produces contact of the active agent with the agent's site of action, i.e., the viral reverse transcriptase, in the body of a mammal. They can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. They can be administered alone, but preferably are administered with a pharmaceutical carrier selected on the basis of the chosen

route of administration and standard pharmaceutical practice.

The dosage administered will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the age, health and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; and the effect desired. A daily dosage of active ingredient can be expected to be about 0.001 to about 1000 milligrams per kilogram of body weight, with the preferred dose being about 0.1 to about 30 mg/kg.

Dosage forms of compositions suitable for administration contain from about 1 mg to about 100 mg of active ingredient per unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition. The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets and powders, or in liquid dosage forms, such as elixirs, syrups and suspensions. It can also be administered parenterally, in sterile liquid dosage forms.

Gelatin capsules contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract. Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts, and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben and chlorobutanol. Suitable pharmaceutical carriers are described in *Remington's Pharmaceutical Sciences, supra*, a standard reference text in this field.

Useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

A large number of unit capsules can be prepared by filling standard two-piece hard gelatin capsules each with 100 mg of powdered active ingredient, 150 mg of lactose, 50 mg of cellulose, and 6 mg magnesium stearic.

Soft Gelatin Capsules

A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil can be prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules should then be washed and dried.

Tablets

A large number of tablets can be prepared by conventional procedures so that the dosage unit is 100 mg of

active ingredient, 0.2 mg of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg of starch and 98.8 mg of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

Suspension

An aqueous suspension can be prepared for oral administration so that each 5 mL contain 25 mg of finely divided active ingredient, 200 mg of sodium carboxymethyl cellulose, 5 mg of sodium benzoate, 1.0 g of sorbitol solution, U.S.P., and 0.025 mg of vanillin.

Injectable

A parenteral composition suitable for administration by injection can be prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol and water. The solution is sterilized by commonly used techniques.

Combination of components (a) and (b)

Each therapeutic agent component of this invention can independently be in any dosage form, such as those described above, and can also be administered in various ways, as described above. In the following description component (b) is to be understood to represent one or more agents as described previously. Thus, if components (a) and (b) are to be treated the same or independently, each agent of component (b) may also be treated the same or independently.

Components (a) and (b) of the present invention may be formulated together, in a single dosage unit (that is, combined together in one capsule, tablet, powder, or liquid, etc.) as a combination product. When component (a) and (b) are not formulated together in a single dosage unit, the component (a) may be administered at the same time as component (b) or in any order; for example component (a) of

this invention may be administered first, followed by administration of component (b), or they may be administered in the revserse order. If component (b) contains more that one agent, e.g., one RT inhibitor and one protease inhibitor, these agents may be administered together or in any order. When not administered at the same time, preferably the administration of component (a) and (b) occurs less than about one hour apart. Preferably, the route of administration of component (a) and (b) is oral. The terms oral agent, oral inhibitor, oral compound, or the like, as used herein, denote compounds which may be orally administered. Although it is preferable that component (a) and component (b) both be administered by the same route (that is, for example, both orally) or dosage form, if desired, they may each be administered by different routes (that is, for example, one component of the combination product may be administered orally, and another component may be administered intravenously) or dosage forms.

As is appreciated by a medical practitioner skilled in the art, the dosage of the combination therapy of the invention may vary depending upon various factors such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration, the age, health and weight of the recipient, the nature and extent of the symptoms, the kind of concurrent treatment, the frequency of treatment, and the effect desired, as described above.

The proper dosage of components (a) and (b) of the present invention will be readily ascertainable by a medical practitioner skilled in the art, based upon the present disclosure. By way of general guidance, typically a daily dosage may be about 100 milligrams to about 1.5 grams of each component. If component (b) represents more than one compound, then typically a daily dosage may be about 100 milligrams to about 1.5 grams of each agent of component (b). By way of general guidance, when the compounds of component (a) and component (b) are administered in

combination, the dosage amount of each component may be reduced by about 70-80% relative to the usual dosage of the component when it is administered alone as a single agent for the treatment of HIV infection, in view of the synergistic effect of the combination.

The combination products of this invention may be formulated such that, although the active ingredients are combined in a single dosage unit, the physical contact between the active ingredients is minimized. In order to minimize contact, for example, where the product is orally administered, one active ingredient may be enteric coated. By enteric coating one of the active ingredients, it is possible not only to minimize the contact between the combined active ingredients, but also, it is possible to control the release of one of these components in the gastrointestinal tract such that one of these components is not released in the stomach but rather is released in the intestines. Another embodiment of this invention where oral administration is desired provides for a combination product wherein one of the active ingredients is coated with a sustained-release material which effects a sustained-release throughout the gastrointestinal tract and also serves to minimize physical contact between the combined active ingredients. Furthermore, the sustained-released component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the formulation of a combination product in which the one component is coated with a sustained and/or enteric release polymer, and the other component is also coated with a polymer such as a low-viscosity grade of hydroxypropyl methylcellulose or other appropriate materials as known in the art, in order to further separate the active components. The polymer coating serves to form an additional barrier to interaction with the other component. In each formulation wherein contact is prevented between components (a) and (b) via a coating or

some other material, contact may also be prevented between the individual agents of component (b).

Dosage forms of the combination products of the present invention wherein one active ingredient is enteric coated can be in the form of tablets such that the enteric coated component and the other active ingredient are blended together and then compressed into a tablet or such that the enteric coated component is compressed into one tablet layer and the other active ingredient is compressed into an additional layer. Optionally, in order to further separate the two layers, one or more placebo layers may be present such that the placebo layer is between the layers of active ingredients. In addition, dosage forms of the present invention can be in the form of capsules wherein one active ingredient is compressed into a tablet or in the form of a plurality of microtablets, particles, granules or non-perils, which are then enteric coated. These enteric coated microtablets, particles, granules or non-perils are then placed into a capsule or compressed into a capsule along with a granulation of the other active ingredient.

These as well as other ways of minimizing contact between the components of combination products of the present invention, whether administered in a single dosage form or administered in separate forms but at the same time or concurrently by the same manner, will be readily apparent to those skilled in the art, based on the present disclosure.

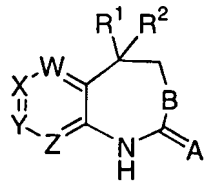
Pharmaceutical kits useful for the treatment of HIV infection, which comprise a therapeutically effective amount of a pharmaceutical composition comprising a compound of component (a) and one or more compounds of component (b), in one or more sterile containers, are also within the ambit of the present invention. Sterilization of the container may be carried out using conventional sterilization methodology well known to those skilled in the art. Component (a) and component (b) may be in the same sterile container or in

separate sterile containers. The sterile containers of materials may comprise separate containers, or one or more multi-part containers, as desired. Component (a) and component (b), may be separate, or physically combined into a single dosage form or unit as described above. Such kits may further include, if desired, one or more of various conventional pharmaceutical kit components, such as for example, one or more pharmaceutically acceptable carriers, additional vials for mixing the components, etc., as will be readily apparent to those skilled in the art. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components, may also be included in the kit.

Obviously, numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that within the scope of the appended claims, the invention may be practiced otherwise than as specifically described herein.

WHAT IS CLAIMED:

1. A compound of formula I:



I

or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein:

A is O or S;

B is selected from O, S, and NR^8;

W is N or CR^3;

X is N or CR^{3a};

Y is N or CR^{3b};

Z is N or CR^{3c};

provided that if two of W, X, Y, and Z are N, then the remaining are other than N;

R^1 is selected from the group C_{1-3} alkyl substituted with 0-7 halogen and cyclopropyl;

R^2 is selected from the group $-R^{2c}$, $-OR^{2c}$, $-OCHR^{2a}R^{2b}$, $-OCH_2CHR^{2a}R^{2b}$, $-O(CH_2)_2CHR^{2a}R^{2b}$, $-OCHR^{2a}C=C-R^{2b}$, $-OCHR^{2a}C=R^{2c}$, $-OCHR^{2a}C\equiv C-R^{2b}$, $-SR^{2c}$, $-SCHR^{2a}R^{2b}$, $-SCH_2CHR^{2a}R^{2b}$, $-S(CH_2)_2CHR^{2a}R^{2b}$, $-SCHR^{2a}C=C-R^{2b}$, $-SCHR^{2a}C=R^{2c}$, $-SCHR^{2a}C\equiv C-R^{2b}$, $-NR^{2a}R^{2c}$, $-NHCHR^{2a}R^{2b}$,

$-NHCH_2CHR^{2a}R^{2b}$, $-NH(CH_2)_2CHR^{2a}R^{2b}$, $-NHCHR^{2a}C=C-R^{2b}$, $-NHCHR^{2a}C=R^{2c}$, and $-NHCHR^{2a}C\equiv C-R^{2b}$;

R^{2a} is selected from the group H, CH_3, CH_2CH_3, $CH(CH_3)_2$, and $CH_2CH_2CH_3$;

R^{2b} is H or R^{2c};

R^{2c} is selected from the group C_{1-6} alkyl substituted with 0-2 R^4, C_{2-5} alkenyl substituted with 0-2 R^4, C_{2-5} alkynyl substituted with 0-1 R^4, C_{3-6} cycloalkyl substituted with 0-2 R^{3d}, phenyl substituted with 0-2 R^{3d}, and 3-6 membered heterocyclic group containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^{3d};

alternatively, the group $-NR^{2a}R^{2c}$ represents a 4-7 membered cyclic amine, wherein 0-1 carbon atoms are replaced by O or NR^5;

R^3 is selected from the group H, C_{1-4} alkyl, -OH, C_{1-4} alkoxy, OCF_3, F, Cl, Br, I, $-NR^5R^{5a}$, $-NO_2$, -CN, $-C(O)R^6$, $-NHC(O)R^7$, $-NHC(O)NR^5R^{5a}$, $-NHSO_2R^{10}$, $-SO_2NR^5R^{5a}$, and a 5-6 membered heteroaromatic ring containing 1-4 heteroatoms selected from the group O, N, and S;

R^{3a} is selected from the group H, C_{1-4} alkyl, -OH, C_{1-4} alkoxy, OCF_3, F, Cl, Br, I, $-NR^5R^{5a}$, $-NO_2$, -CN, $-C(O)R^6$, $-NHC(O)R^7$, $-NHC(O)NR^5R^{5a}$, $-NHSO_2R^{10}$, $-SO_2NR^5R^{5a}$, and a 5-6 membered heteroaromatic ring containing 1-4 heteroatoms selected from the group O, N, and S;

alternatively, R^3 and R^{3a} together form $-OCH_2O-$;

R^{3b} is selected from the group H, C_{1-4} alkyl, -OH, C_{1-4} alkoxy, OCF_3, F, Cl, Br, I, $-NR^5R^{5a}$, $-NO_2$, -CN, $-C(O)R^6$, $-NHC(O)R^7$, $-NHC(O)NR^5R^{5a}$, $-NHSO_2R^{10}$, and $-SO_2NR^5R^{5a}$;

alternatively, R^{3a} and R^{3b} together form $-OCH_2O-$;

R^{3c} is selected from the group H, C_{1-4} alkyl, -OH, C_{1-4} alkoxy, OCF_3, F, Cl, Br, I, $-NR^5R^{5a}$, $-NO_2$, -CN, $-C(O)R^6$, $-NHC(O)R^7$, $-NHC(O)NR^5R^{5a}$, $-NHSO_2R^{10}$, and $-SO_2NR^5R^{5a}$;

alternatively, R^{3b} and R^{3c} together form $-OCH_2O-$;

R^{3d}, at each occurrence, is independently selected from the group C_{1-4} alkyl, -OH, C_{1-4} alkoxy, OCF_3, F, Cl, Br, I, $-NR^5R^{5a}$, $-NO_2$, -CN, $-C(O)R^6$, $-NHC(O)R^7$, $-NHC(O)NR^5R^{5a}$, $-NHSO_2R^{10}$, and $-SO_2NR^5R^{5a}$;

R^{3e}, at each occurrence, is independently selected from the group C_{1-4} alkyl, -OH, C_{1-4} alkoxy, OCF_3, F, Cl, Br, I, $-NR^5R^{5a}$, $-NO_2$, -CN, $-C(O)R^6$, $-NHC(O)R^7$, $-NHC(O)NR^5R^{5a}$, $-NHSO_2R^{10}$, and $-SO_2NR^5R^{5a}$;

R^{3f}, at each occurrence, is independently selected from the group C_{1-4} alkyl, -OH, C_{1-4} alkoxy, OCF_3, F, Cl, Br, I, $-NR^5R^{5a}$, $-NO_2$, -CN, $-C(O)R^6$, $-NHC(O)R^7$, $-NHC(O)NR^5R^{5a}$, $-NHSO_2R^{10}$, and $-SO_2NR^5R^{5a}$;

R^{3g}, at each occurrence, is independently selected from the group C_{1-4} alkyl, -OH, C_{1-4} alkoxy, OCF_3, F, Cl, Br, I, $-NR^5R^{5a}$, $-NO_2$, -CN, $-C(O)R^6$, $-NHC(O)R^7$, $-NHC(O)NR^5R^{5a}$, $-NHSO_2R^{10}$, $-SO_2NR^5R^{5a}$, C_{3-10} carbocycle substituted with 0-3 R^{3f} and a 5-10 membered heterocyclic group

containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-3 R^{3f}; and,

R^4 is selected from the group F, Cl, Br, I, C_{1-6} alkyl substituted with 0-2 R^{3e}, C_{3-10} carbocycle substituted with 0-2 R^{3e}, phenyl substituted with 0-5 R^{3e}, and a 5-10 membered heterocyclic group containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^{3e};

R^5 and R^{5a} are independently selected from the group H and C_{1-4} alkyl;

alternatively, R^5 and R^{5a}, together with the nitrogen to which they are attached, combine to form a 5-6 membered ring containing 0-1 O or N atoms;

R^6 is selected from the group H, OH, C_{1-4} alkyl, C_{1-4} alkoxy, and NR^5R^{5a};

R^7 is selected from the group C_{1-3} alkyl and C_{1-3} alkoxy;

R^8 is selected from the group H, OR^9, SR^9, NR^5R^9, C_{1-6} alkyl substituted with 0-3 R^{3g}, C_{2-6} alkenyl substituted with 0-3 R^{3g}, C_{2-6} alkynyl substituted with 0-3 R^{3g}, C_{3-5} cycloalkyl substituted with 0-2 R^{3f}, phenyl substituted with 0-5 R^{3f}, and a 5-6 membered heterocyclic group containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^{3f};

R^9 is selected from the group C_{3-10} carbocycle substituted with 0-5 R^{3f} and a 5-10 membered heterocyclic group containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^{3f}; and,

R^{10} is selected from the group C_{1-4} alkyl and phenyl.

2. A compound according to Claim 1, wherein:

B is NR^8;

R^1 is selected from the group C_{1-3} alkyl substituted with 1-7 halogen and cyclopropyl;

R^2 is selected from the group $-R^{2c}$, $-OR^{2c}$, $-OCHR^{2a}R^{2b}$, $-OCH_2CHR^{2a}R^{2b}$, $-O(CH_2)_2CHR^{2a}R^{2b}$, $-OCHR^{2a}C=C-R^{2b}$, $-OCHR^{2a}C=R^{2c}$, $-OCHR^{2a}C\equiv C-R^{2b}$, $-SR^{2c}$, $-SCHR^{2a}R^{2b}$, $-SCH_2CHR^{2a}R^{2b}$, $-S(CH_2)_2CHR^{2a}R^{2b}$, $-SCHR^{2a}C=C-R^{2b}$, $-SCHR^{2a}C=R^{2c}$, and $-SCHR^{2a}C\equiv C-R^{2b}$;

R^{2a} is selected from the group H, CH_3, CH_2CH_3, $CH(CH_3)_2$, and $CH_2CH_2CH_3$;

R^{2b} is H or R^{2c};

R^{2c} is selected from the group C_{1-5} alkyl substituted with 0-2 R^4, C_{2-5} alkenyl substituted with 0-2 R^4, C_{2-5} alkynyl substituted with 0-1 R^4, C_{3-6} cycloalkyl substituted with 0-2 R^{3d}, and phenyl substituted with 0-2 R^{3d};

R^3, at each occurrence, is independently selected from the group H, C_{1-4} alkyl, OH, C_{1-4} alkoxy, F, Cl, Br, I, NR^5R^{5a}, NO_2, -CN, $C(O)R^6$, $NHC(O)R^7$, $NHC(O)NR^5R^{5a}$, and a 5-6 membered heteroaromatic ring containing 1-4 heteroatoms selected from the group O, N, and S;

R^{3a}, at each occurrence, is independently selected from the group H, C_{1-4} alkyl, OH, C_{1-4} alkoxy, F, Cl, Br, I, NR^5R^{5a}, NO_2, -CN, $C(O)R^6$, $NHC(O)R^7$, $NHC(O)NR^5R^{5a}$, and a 5-6 membered heteroaromatic ring containing 1-4 heteroatoms selected from the group O, N, and S;

alternatively, R^3 and R^{3a} together form $-OCH_2O-$;

R^{3b}, at each occurrence, is independently selected from the group H, C_{1-4} alkyl, OH, C_{1-4} alkoxy, F, Cl, Br, I, NR^5R^{5a}, NO_2, -CN, $C(O)R^6$, $NHC(O)R^7$, and $NHC(O)NR^5R^{5a}$;

alternatively, R^{3a} and R^{3b} together form $-OCH_2O-$;

R^4 is selected from the group Cl, F, C_{1-4} alkyl substituted with 0-2 R^{3e}, C_{3-5} carbocycle substituted with 0-2 R^{3e}, phenyl substituted with 0-5 R^{3e}, and a 5-6 membered heterocyclic group containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^{3e};

R^5 and R^{5a} are independently selected from the group H, CH_3 and C_2H_5;

R^6 is selected from the group H, OH, CH_3, C_2H_5, OCH_3, OC_2H_5, and NR^5R^{5a};

R^7 is selected from the group CH_3, C_2H_5, $CH(CH_3)_2$, OCH_3, OC_2H_5, and $OCH(CH_3)_2$; and,

R^8 is selected from the group H, cyclopropyl, CH_3, C_2H_5, and $CH(CH_3)_2$.

3. A compound according to Claim 2, wherein:

R^1 is selected from the group CF_3, C_2F_5, and cyclopropyl;

R^2 is selected from the group $-R^{2c}$, $-OR^{2c}$, $-OCHR^{2a}R^{2b}$, $-OCH_2CHR^{2a}R^{2b}$, $-OCHR^{2a}C{=}C-R^{2b}$, $-OCHR^{2a}C{=}R^{2c}$, $-OCHR^{2a}C{\equiv}C-R^{2b}$, $-SR^{2c}$, $-SCHR^{2a}R^{2b}$, $-SCH_2CHR^{2a}R^{2b}$, $-SCHR^{2a}C{=}C-R^{2b}$, $-SCHR^{2a}C{=}R^{2c}$, and $-SCHR^{2a}C{\equiv}C-R^{2b}$;

R^{2a} is selected from the group H, CH_3, CH_2CH_3, $CH(CH_3)_2$, and $CH_2CH_2CH_3$;

R^{2b} is H or R^{2c};

R^{2c} is selected from the group C_{1-3} alkyl substituted with 0-2 R^4, C_{2-3} alkenyl substituted with 0-2 R^4, C_{2-3} alkynyl substituted with 0-1 R^4, and C_{3-6} cycloalkyl substituted with 0-2 R^{3d};

R^3, at each occurrence, is independently selected from the group H, C_{1-3} alkyl, OH, C_{1-3} alkoxy, F, Cl, Br, I, NR^5R^{5a}, NO_2, -CN, $C(O)R^6$, $NHC(O)R^7$, and $NHC(O)NR^5R^{5a}$;

alternatively, R^3 and R^{3a} together form $-OCH_2O-$;

R^{3b} is H;

R^{3c} is H;

R^{3e}, at each occurrence, is independently selected from the group H, C_{1-4} alkyl, -OH, C_{1-4} alkoxy, OCF_3, F, Cl, $-NR^5R^{5a}$, $-C(O)R^6$, and $-SO_2NR^5R^{5a}$;

R^4 is selected from the group Cl, F, C_{1-4} alkyl substituted with 0-1 R^{3e}, C_{3-5} carbocycle substituted with 0-2 R^{3e}, phenyl substituted with 0-2 R^{3e}, and a 5-6 membered heterocyclic group containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-1 R^{3e};

R^5 and R^{5a} are independently selected from the group H, CH_3 and C_2H_5;

R^6 is selected from the group H, OH, CH_3, C_2H_5, OCH_3, OC_2H_5, and NR^5R^{5a};

R^7 is selected from the group CH_3, C_2H_5, OCH_3, and OC_2H_5; and,

R^8 is selected from the group H, cyclopropyl, CH_3, and C_2H_5.

4. A compound according to Claim 3, wherein:

R^1 is CF_3;

R^2 is selected from the group $-R^{2c}$, $-OR^{2c}$, $-OCH_2R^{2b}$, $-OCH_2CH_2R^{2b}$, $-OCH_2C{=}C-R^{2b}$, $-OCH_2C{\equiv}C-R^{2b}$, $-SR^{2c}$, $-SCH_2R^{2b}$, $-SCH_2CH_2R^{2b}$, $-SCH_2C{=}C-R^{2b}$, and $-SCH_2C{\equiv}C-R^{2b}$;

R^{2b} is H or R^{2c};

R^{2c} is selected from the group methyl substituted with 0-2 R^4, ethyl substituted with 0-2 R^4, propyl substituted with 0-2 R^4, ethenyl substituted with 0-2 R^4, 1-propenyl substituted with 0-2 R^4, 2-propenyl substituted with 0-2 R^4, ethynyl substituted with 0-2 R^4, 1-propynyl

substituted with 0-2 R^4, 2-propynyl substituted with 0-2 R^4, and cyclopropyl substituted with 0-1 R^{3d};

R^3, at each occurrence, is independently selected from the group C_{1-3} alkyl, OH, C_{1-3} alkoxy, F, Cl, NR^5R^{5a}, NO_2, -CN, and $C(O)R^6$;

alternatively, R^3 and R^{3a} together form $-OCH_2O-$;

R^{3d}, at each occurrence, is independently selected from the group CH_3, -OH, OCH_3, OCF_3, F, Cl, and $-NR^5R^{5a}$;

R^{3e}, at each occurrence, is independently selected from the group CH_3, -OH, OCH_3, OCF_3, F, Cl, and $-NR^5R^{5a}$;

R^4 is selected from the group Cl, F, CH_3, CH_2CH_3, cyclopropyl substituted with 0-1 R^{3e}, 1-methyl-cyclopropyl substituted with 0-1 R^{3e}, cyclobutyl substituted with 0-1 R^{3e}, phenyl substituted with 0-2 R^{3e}, and a 5-6 membered heterocyclic group containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-1 R^{3e}, wherein the heterocyclic group is selected from the group 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-oxazolyl, 2-thiazolyl, 4-isoxazolyl, and 2-imidazolyl;

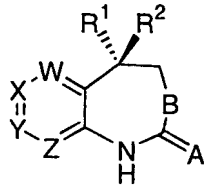
R^5 and R^{5a} are independently selected from the group H, CH_3 and C_2H_5;

R^6 is selected from the group H, OH, CH_3, C_2H_5, OCH_3, OC_2H_5, and NR^5R^{5a};

R^7 is selected from the group CH_3, C_2H_5, OCH_3, and OC_2H_5; and,

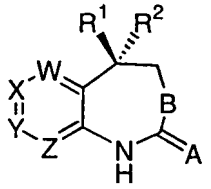
R^8 is selected from the group H, cyclopropyl, and C_2H_5.

5. A compound according to Claim 4, wherein the compound is of formula Ia



Ia.

6. A compound according to Claim 4, wherein the compound is of formula Ib:



Ib.

7. A compound according to Claim 1, wherein the compound is selected from the group:

7-Chloro-5-(2-cyclopropylethynyl)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

6,7-difluoro-5-(2-cyclopropylethynyl)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-5-(2-cyclopropylethenyl)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-5-(2-cyclopropylethynyl)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-thione;

7-Chloro-5-(2-n-butyl)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-5-(2-cyclopropylethynyl)-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-5-(2-cyclopropylethynyl)-1,5-dihydro-3-ethyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-5-(2-cyclopropylethynyl)-1,5-dihydro-3-cyclopropyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-5-cyclopropylmethyloxy-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-5-(3-methyl-2-butenyloxy)-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-5-(3-allyloxy)-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-5-(3,3-dichloro-2-propenyloxy)-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-5-(2-propynyloxy)-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-5-(2-fluoro-6-methoxybenzyloxy)-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-5-(cyclopropylmethyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-(cyclopropylmethyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-3-cyclopropyl-5-(cyclopropylmethoxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-3-cyclopropyl-5-(cyclopropylmethoxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-3-cyclopropyl-5-propyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-3-cyclopropyl-5-propylthio-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-3-cyclopropyl-5-allylthio-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-3-cyclopropyl-5-allyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-3-cyclopropyl-5-(3-methyl-2-butenyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-3-cyclopropyl-5-cyclobutylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-3-cyclopropyl-5-(1-methylcyclopropyl)methyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-3-cyclopropyl-5-(2-pyridyl)methyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-3-isopropyl-5-cyclopropylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-3-cyclobutyl-5-cyclopropylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-5-(cyclopropylmethoxy)-1,5-dihydro-3-ethyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-(cyclopropylmethyloxy)-1,5-dihydro-3-ethyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-3-ethyl-5-(3-methyl-2-butenyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-3-ethyl-5-allylthio-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-3-ethyl-5-cyclobutylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-3-ethyl-5-cyclopropylmethylthio-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-3-ethyl-5-(1-methylcyclopropyl)methyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-3-propyl-5-cyclopropylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Fluoro-5-(cyclopropylmethoxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Fluoro-3-ethyl-5-cyclopropylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Fluoro-5-(cyclobutylmethoxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Fluoro-3-ethyl-5-cyclobutylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-5-[2-(1-methylcyclopropyl)ethynyl]-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-5-cyclobutylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-5-(3-methyl-2-butenyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-5-(phenylmethyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-5-[(2-pyridyl)methyloxy]-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-5-[(1-methylcyclopropyl)methyoxy]-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-5-(3-methylphenyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-5-(cyclopropylmethylthio)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

7-Chloro-5-(propylthio)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one; and,

7-Chloro-5-(2-propenylthio)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

or a pharmaceutically acceptable salt form thereof.

8. A compound according to Claim 1, wherein the compound is selected from the group:

(S)-7-Chloro-5-(2-cyclopropylethynyl)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-6,7-difluoro-5-(2-cyclopropylethynyl)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-(2-cyclopropylethenyl)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-(2-cyclopropylethynyl)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-thione;

(S)-7-Chloro-5-(2-n-butyl)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-(2-cyclopropylethynyl)-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-(2-cyclopropylethynyl)-1,5-dihydro-3-ethyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-(2-cyclopropylethynyl)-1,5-dihydro-3-cyclopropyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-cyclopropylmethyloxy-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-(3-methyl-2-butenyloxy)-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-(3-allyloxy)-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-(3,3-dichloro-2-propenyloxy)-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-(2-propynyloxy)-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-(2-fluoro-6-methoxybenzyloxy)-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-(cyclopropylmethyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-(cyclopropylmethyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-3-cyclopropyl-5-(cyclopropylmethoxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-3-cyclopropyl-5-(cyclopropylmethoxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-3-cyclopropyl-5-propyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-3-cyclopropyl-5-propylthio-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-3-cyclopropyl-5-allylthio-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-3-cyclopropyl-5-allyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-3-cyclopropyl-5-(3-methyl-2-butenyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-3-cyclopropyl-5-cyclobutylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-3-cyclopropyl-5-(1-methylcyclopropyl)methyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-3-cyclopropyl-5-(2-pyridyl)methyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-3-isopropyl-5-cyclopropylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-3-cyclobutyl-5-cyclopropylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-(cyclopropylmethoxy)-1,5-dihydro-3-ethyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-(cyclopropylmethyloxy)-1,5-dihydro-3-ethyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-3-ethyl-5-(3-methyl-2-butenyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-3-ethyl-5-allylthio-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-3-ethyl-5-cyclobutylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-3-ethyl-5-cyclopropylmethylthio-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-3-ethyl-5-(1-methylcyclopropyl)methyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-3-propyl-5-cyclopropylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Fluoro-5-(cyclopropylmethoxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Fluoro-3-ethyl-5-cyclopropylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Fluoro-5-(cyclobutylmethoxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Fluoro-3-ethyl-5-cyclobutylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-[2-(1-methylcyclopropyl)ethynyl]-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-cyclobutylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-(3-methyl-2-butenyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-(phenylmethyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-[(2-pyridyl)methyloxy]-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-[(1-methylcyclopropyl)methyoxy]-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-(3-methylphenyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-(cyclopropylmethylthio)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(S)-7-Chloro-5-(propylthio)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one; and,

(S)-7-Chloro-5-(2-propenylthio)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

or a pharmaceutically acceptable salt form thereof.

9. A compound according to Claim 1, wherein the compound is selected from the group:

(R)-7-Chloro-5-(2-cyclopropylethynyl)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-6,7-difluoro-5-(2-cyclopropylethynyl)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-(2-cyclopropylethenyl)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-(2-cyclopropylethynyl)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-thione;

(R)-7-Chloro-5-(2-n-butyl)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-(2-cyclopropylethynyl)-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-(2-cyclopropylethynyl)-1,5-dihydro-3-ethyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-(2-cyclopropylethynyl)-1,5-dihydro-3-cyclopropyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-cyclopropylmethyloxy-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-(3-methyl-2-butenyloxy)-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-(3-allyloxy)-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-(3,3-dichloro-2-propenyloxy)-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-(2-propynyloxy)-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-(2-fluoro-6-methoxybenzyloxy)-1,5-dihydro-3-methyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-(cyclopropylmethyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-(cyclopropylmethyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-3-cyclopropyl-5-(cyclopropylmethoxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-3-cyclopropyl-5-(cyclopropylmethoxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-3-cyclopropyl-5-propyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-3-cyclopropyl-5-propylthio-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-3-cyclopropyl-5-allylthio-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-3-cyclopropyl-5-allyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-3-cyclopropyl-5-(3-methyl-2-butenyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-3-cyclopropyl-5-cyclobutylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-3-cyclopropyl-5-(1-methylcyclopropyl)methyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-3-cyclopropyl-5-(2-pyridyl)methyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-3-isopropyl-5-cyclopropylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-3-cyclobutyl-5-cyclopropylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-(cyclopropylmethoxy)-1,5-dihydro-3-ethyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-(cyclopropylmethyloxy)-1,5-dihydro-3-ethyl-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-3-ethyl-5-(3-methyl-2-butenyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-3-ethyl-5-allylthio-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-3-ethyl-5-cyclobutylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-3-ethyl-5-cyclopropylmethylthio-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-3-ethyl-5-(1-methylcyclopropyl)methyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-3-propyl-5-cyclopropylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Fluoro-5-(cyclopropylmethoxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Fluoro-3-ethyl-5-cyclopropylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Fluoro-5-(cyclobutylmethoxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Fluoro-3-ethyl-5-cyclobutylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-[2-(1-methylcyclopropyl)ethynyl]-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-cyclobutylmethyloxy-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-(3-methyl-2-butenyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-(phenylmethyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-[(2-pyridyl)methyloxy]-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-[(1-methylcyclopropyl)methyoxy]-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-(3-methylphenyloxy)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-(cyclopropylmethylthio)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

(R)-7-Chloro-5-(propylthio)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one; and,

(R)-7-Chloro-5-(2-propenylthio)-1,5-dihydro-5-(trifluoromethyl)-1,3-benzodiazepin-2-one;

or a pharmaceutically acceptable salt form thereof.

10. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound according to Claim 1, 2, 3, 4, 5, 6, 7, 8, or 9 or pharmaceutically acceptable salt form thereof.

11. A method of treating HIV infection which comprises administering to a host in need of such treatment a therapeutically effective amount of a compound according to Claim 1, 2, 3, 4, 5, 6, 7, 8, or 9 or pharmaceutically acceptable salt form thereof.

12. A method of treating HIV infection which comprises administering, in combination, to a host in need thereof a therapeutically effective amount of:

(a) a compound according to Claim 1, 2, 3, 4, 5, 6, 7, 8, or 9; and,

(b) at least one compound selected from the group consisting of HIV reverse transcriptase inhibitors and HIV protease inhibitors.

13. A method according to Claim 10, wherein the reverse transcriptase inhibitor is selected from the group AZT, ddC, ddI, d4T, 3TC, DPC082, DPC083, DPC961, DPC963, AG1549 delavirdine, efavirenz, nevirapine, Ro 18,893, trovirdine, MKC-442, HBY 097, ACT, UC-781, UC-782, RD4-2025, and MEN 10979, and the protease inhibitor is selected from the group saquinavir, ritonavir, indinavir, amprenavir, nelfinavir, palinavir, BMS-232623, GS3333, KNI-413, KNI-272, LG-71350, CGP-61755, PD 173606, PD 177298, PD 178390, PD 178392, U-140690, and ABT-378.

14. A method according to Claim 11, wherein the reverse transcriptase inhibitor is selected from the group AZT, efavirenz, and 3TC and the protease inhibitor is selected from the group saquinavir, ritonavir, nelfinavir, and indinavir.

15. A method according to Claim 12 wherein the reverse transcriptase inhibitor is AZT.

16. A method according to Claim 12, wherein the protease inhibitor is indinavir.

17. A pharmaceutical kit useful for the treatment of HIV infection, which comprises a therapeutically effective amount of:

(a) a compound according to Claim 1, 2, 3, 4, 5, 6, 7, 8, or 9 or a pharmaceutically acceptable salt form thereof; and,

(b) at least one compound selected from the group consisting of HIV reverse transcriptase inhibitors and HIV protease inhibitors, in one or more sterile containers.

18. A compound according to Claim 1, 2, 3, 4, 5, 6, 7, 8, or 9 or pharmaceutically acceptable salt forms thereof for use in therapy.

19. Use of compounds according to Claim 1, 2, 3, 4, 5, 6, 7, 8, or 9 or pharmaceutically acceptable salt forms thereof for the manufacture of a medicament for the treatment of HIV.

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/US 99/13872

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D243/04 A61K31/55 C07D401/12 C07D471/04 C07D487/04
C07D267/06 C07D281/02 C07D405/06 C07D409/06 C07D401/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 530 994 A (MERCK) 10 March 1993 (1993-03-10) cited in the application claims 1,8	1,10
A	US 5 532 357 A (RODGERS ET AL.) 2 July 1996 (1996-07-02) column 42, line 18 - line 58; claim 1	1,8

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 October 1999	08/11/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Alfaro Faus, I

INTERNATIONAL SEARCH REPORT

rnational application No.
PCT/US 99/13872

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 11-16 and 19
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 11-16 and 19 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

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